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ARTICLES

27 Dexamethasone and Bacterial Meningitis—A Meta-analysis of Randomized Controlled Trials
B J GEIMAN and A L SMITH

32 Risk for AIDS in Multiethnic Neighborhoods in San Francisco, California—The Population-Based AMEN Study
M T FULLILOVE, J WILEY, R E FULLILOVE, E GOLDEN, J CATANIA, J PETERSON, K GARRETT, D SIEGEL, B MARIN, S KEGELES, T COATES, and S HULLEY

41 Health Care Use by Human Immunodeficiency Virus-Infected Students at a California Student Health Service
C L BENNETT, H CHANG, D SHLIAN, J A DAWSON, and B R EDLIN

44 Factors Influencing Family Physicians to Continue Providing Obstetric Care
T S NESBITT, N B KAHN, J L TANJI, and J E SCHERGER

CONFERENCES AND REVIEWS

48 Endoscopic Laser Therapy in Gastroenterology
J PRITIKIN, D WEINMAN, A HARMATZ, and H YOUNG

55 Do We Need an Intravenous Fluoroquinolone?
D S MADDIX and L WARNER

EPITOMES

60 Important Advances in Nuclear Medicine

ALERTS, NOTICES, AND CASE REPORTS

64 Chronic Atypical Seizure Disorder and Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism
J C FAIG, J KALINYAK, R MARCUS, and D FELDMAN

65 Hypokalemia as a Cause of Tetany
M J AULT and J GEIDERMAN

67 Current Management of Diabetic Retinopathy
E AI

COMMENTARY

71 Global Health Leadership—A Continuing US Challenge
A SOMMER

74 Scientific Medicine, Social Ills, and Child Health
R E BEHRMAN

77 Playing the Cost-Containment Game
W O ROBERTSON

79 Earthquakes and the Office-Based Surgeon
W A CONOVER

EDITORIALS

83 You Light Up My Life . . . and Liver—Gastroenterologic Laser Therapy in the 1990s • Eight Years and Counting—What Can Americans Do? • Meta-analysis Redux—Steroids and Meningitis Revisited

CORRESPONDENCE

87 History and Diagnosis • If Syncope, Think Long QT • Correction

LESSONS FROM THE PRACTICE

88 Quality Medicine
R L GOLDSTONE

OTHER FEATURES

13 Subscription Information

20 In Memoriam

22 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

95 Instructions for Authors

97 Classified Advertising

106 Western State Medical Associations' Meetings

Poems: 40, 78, 82

Detailed Table of Contents: 2, 6, 11

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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Drug Interactions. No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine

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Pregnancy Category C: ROGAINE should not be used by pregnant women

Labor and Delivery: The effects are not known

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Postmenopausal Use: Efficacy in postmenopausal women has not been studied

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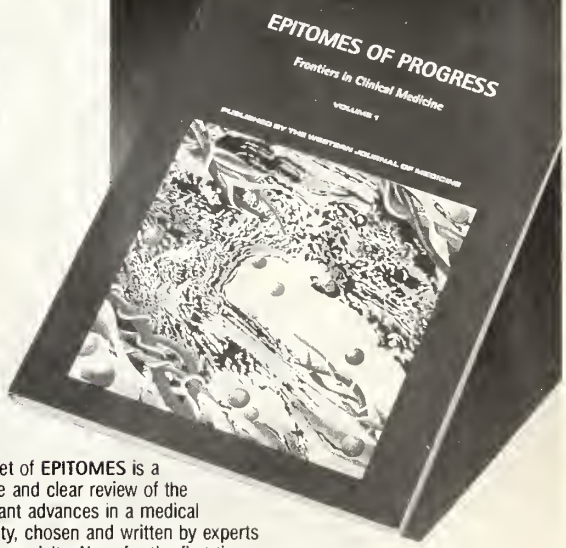

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(Continued from Page 2)

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Nuclear Medicine

Items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

60 **Use of Thallium 201 in Tumor Evaluation**
ALAN D. WAXMAN, MD

60 **Technetium 99m-Hexamethyl Propyleneamine Oxime-Labeled Leukocytes for Diagnosis of Infection**
FREDERICK L. DATZ, MD

61 **Radionuclide Evaluation of Brain Death**
C. L. LUTRIN, MB, ChB

62 **Radionuclide Therapy for Thyroid Disease**
I. ROSS McDOUGALL, MB, ChB, PhD

62 **Diagnostic and Therapeutic Uses of Metaiodobenzylguanidine**
MARGUERITE T. PARISI, MD, and ROBERT S. HATTNER, MD

ALERTS, NOTICES, AND CASE REPORTS

64 **Chronic Atypical Seizure Disorder and Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism**
JEFFREY C. FAIG, MD; JUDITH KALINYAK, MD; ROBERT MARCUS, MD; and DAVID FELDMAN, MD

From the Division of Endocrinology, Stanford University School of Medicine, Stanford, California, and the Department of Endocrinology, San Francisco General Hospital Medical Center, San Francisco, California.

65 **Hypokalemia as a Cause of Tetany**
MARK J. AULT, MD, and JOEL GEIDERMAN, MD

From the Ambulatory Care Center and the Department of Emergency Medicine, Cedars-Sinai Medical Center, and University of California, Los Angeles, School of Medicine.

67 **Current Management of Diabetic Retinopathy**
EVERETT AI, MD

From the Retina Unit, Department of Ophthalmology, California Pacific Medical Center, San Francisco, California.

COMMENTARY

71 **Global Health Leadership—A Continuing US Challenge**
ALFRED SOMMER, MD, MHS

From the Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland.

74 **Scientific Medicine, Social Ills, and Child Health**
RICHARD E. BEHRMAN, MD

From the Center for the Future of Children, The David and Lucile Packard Foundation, Los Altos, and the Departments of Pediatrics, Stanford University School of Medicine, Stanford, and University of California, San Francisco, School of Medicine.

77 **Playing the Cost-Containment Game**
WILLIAM O. ROBERTSON, MD

From the Department of Pediatrics, Children's Hospital and Medical Center and University of Washington School of Medicine, and the Seattle Poison Center and Washington Poison Network, Seattle.

79 **Earthquakes and the Office-Based Surgeon**
WILLIAM A. CONOVER, MD

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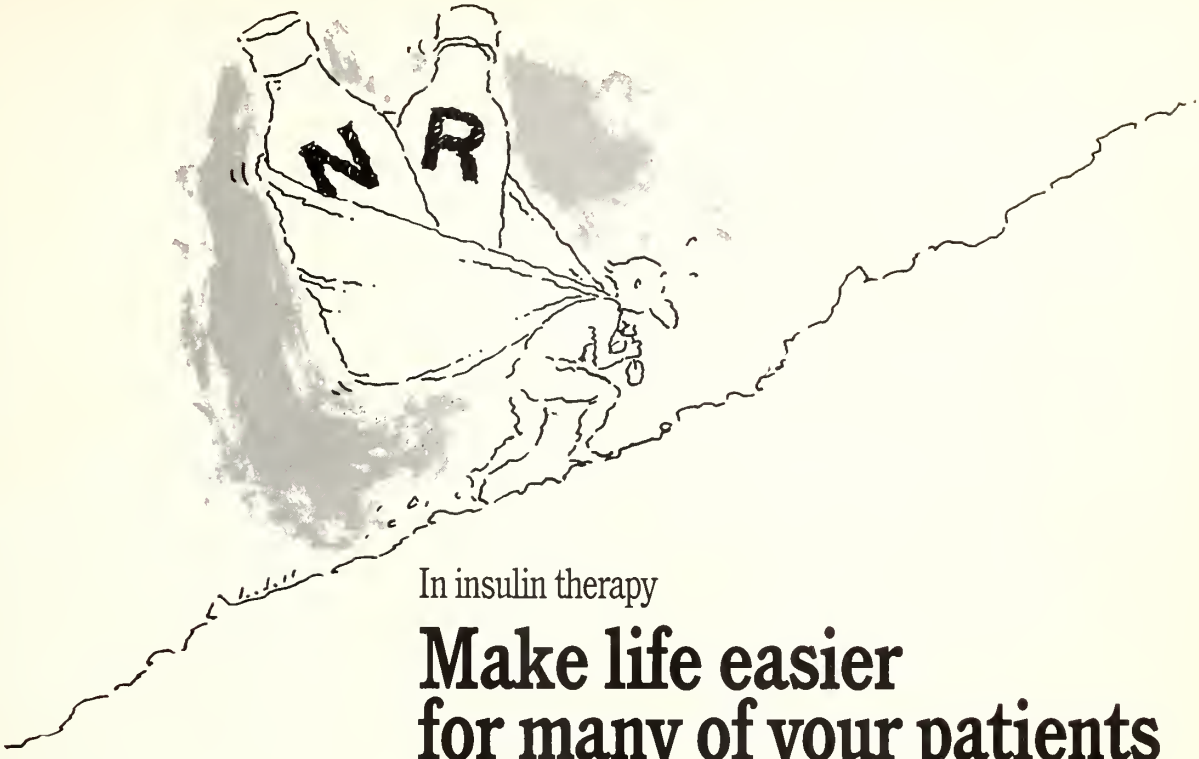
(Continued on Page 11)



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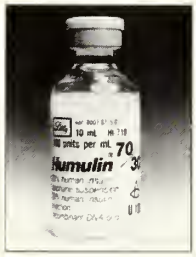

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(Fullilove MT, Wiley J, Fullilove RE, et al: Risk for AIDS in multiethnic neighborhoods of San Francisco, California—The population-based AMEN study. West J Med 1992 Jul; 157:32-40)

To examine the actual and potential spread of human immunodeficiency virus (HIV) from an acquired immunodeficiency syndrome (AIDS) epicenter to surrounding neighborhoods, we studied the prevalence of the viral infection and AIDS risk behaviors from 1988 to 1989 in a representative sample of unmarried whites, African Americans, and Hispanics living in San Francisco. We surveyed 1,770 single men and women aged 20 to 44 years (a 64% response rate) in a random household sample drawn from 3 neighborhoods of varying geographic and cultural proximity to the Castro District where the San Francisco epidemic began. Of 1,369 with blood tests, 69 (5%) had HIV antibodies; all but 5 of these reported either homosexual activity (32% HIV-positive; 95% confidence interval [CI] = 23%, 41%), injection drug use (5% HIV-positive; CI = 1%, 14%), or both (59% HIV-positive; CI 42%, 74%). Homosexual activity was more common among white men than among African-American or Hispanic men, but the proportion of those infected was similar in the 3 races. Both the prevalence of homosexually active men and the proportion infected were much lower in the 2 more outlying neighborhoods.

Risk behaviors in the past year for acquiring HIV heterosexually—sex with an HIV-infected person or homosexually active man or injection drug user, unprotected sexual intercourse with more than 4 partners, and (as a proxy) having a sexually transmitted disease—were assessed in 1,573 neighborhood residents who were themselves neither homosexually active men nor injection drug users. The prevalence of reporting at least 1 of these risk behaviors was 12% overall, and race-gender estimates ranged from 5% among Hispanic women to 21% among white women. We conclude that in San Francisco, infection with HIV is rare among people who are neither homosexually active nor injection drug users, but the potential for the spread of infection is substantial, as 12% of this group reported important risk behaviors for acquiring the virus heterosexually.

AIDS **AIDS AND MINORITIES**
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HIV INFECTION **AMEN STUDY**

(Fullilove MT, Wiley J, Fullilove RE, et al: Risk for AIDS in multiethnic neighborhoods of San Francisco, California—The population-based AMEN study. West J Med 1992 Jul; 157:32-40)

To examine the actual and potential spread of human immunodeficiency virus (HIV) from an acquired immunodeficiency syndrome (AIDS) epicenter to surrounding neighborhoods, we studied the prevalence of the viral infection and AIDS risk behaviors from 1988 to 1989 in a representative sample of unmarried whites, African Americans, and Hispanics living in San Francisco. We surveyed 1,770 single men and women aged 20 to 44 years (a 64% response rate) in a random household sample drawn from 3 neighborhoods of varying geographic and cultural proximity to the Castro District where the San Francisco epidemic began. Of 1,369 with blood tests, 69 (5%) had HIV antibodies; all but 5 of these reported either homosexual activity (32% HIV-positive; 95% confidence interval [CI] = 23%, 41%), injection drug use (5% HIV-positive; CI = 1%, 14%), or both (59% HIV-positive; CI 42%, 74%). Homosexual activity was more common among white men than among African-American or Hispanic men, but the proportion of those infected was similar in the 3 races. Both the prevalence of homosexually active men and the proportion infected were much lower in the 2 more outlying neighborhoods.

Risk behaviors in the past year for acquiring HIV heterosexually—sex with an HIV-infected person or homosexually active man or injection drug user, unprotected sexual intercourse with more than 4 partners, and (as a proxy) having a sexually transmitted disease—were assessed in 1,573 neighborhood residents who were themselves neither homosexually active men nor injection drug users. The prevalence of reporting at least 1 of these risk behaviors was 12% overall, and race-gender estimates ranged from 5% among Hispanic women to 21% among white women. We conclude that in San Francisco, infection with HIV is rare among people who are neither homosexually active nor injection drug users, but the potential for the spread of infection is substantial, as 12% of this group reported important risk behaviors for acquiring the virus heterosexually.

AIDS **AIDS AND MINORITIES**
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BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. **Acute Hepatic Injury**. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions report placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZE Capsules involving over 3000 patients, the most common events (ie, gr than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asth (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1. nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%

Cardiovascular: Angina, arrhythmia, AV block (second- or third-deg bundle branch block, congestive heart failure, ECG abnormal hypotension, palpitations, syncope, tachycardia, ventric extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnorm hallucinations, insomnia, nervousness, paresthesia, personality cha somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see he warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irrital hyperglycemia, hyperuricemia, impotence, muscle cramps, congestion, nocturia, osteoarticular pain, polyuria, sexual difficulti

The following postmarketing events have been reported infrequen patients receiving CARDIZEM: alopecia, erythema multiforme, exfoli dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic an increased bleeding time, leukopenia, purpura, retinopathy, thrombocytopenia. In addition, events such as myocardial infarction been observed which are not readily distinguishable from the natural hi of the disease in these patients. A number of well-documented cas generalized rash, characterized as leukocytoclastic vasculitis, have reported. However, a definitive cause and effect relationship between t events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 18 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 1

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release ca of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 1

CARDIZEM® CD Product Information as of October 1991

CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Mattso Prevey ML, et al. *JAMA* 1989;261(22):3273-3274.

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(Continued from Page 6)

EDITORIALS

83 **You Light Up My Life . . . and Liver—Gastroenterologic Laser Therapy in the 1990s**
RICHARD A. KOZAREK, MD
Dr Kozorek is Chief of Gostroenterology, Virginio Mason Clinic, ond Clinicol Professor of Medicine, University of Washington School of Medicine, Seottle.

84 **Eight Years and Counting—What Can Americans Do?**
ANVAR VELJI, MD, FRCP, FACP(C)
Dr Velji is Associote Clinicol Professor of Medicine, University of Colifornio, Dovis, Medicol Center, ond Division of Infectious Diseoses, Deportment of Medicine, Koiser Permonente Medicol Center, Socromento, Colifornio.

84 **Meta-analysis Redux—Steroids and Meningitis Revisited**
PETER L. HAVENS, MD, MS
Dr Hovens is Associote Professor of Pediatrics ond Biostotistics/Clinicol Epidemiology, Division of Criticol Core ond Infectious Diseoses, Medicol College of Wisconsin ond Children's Hospitol of Wisconsin, Milwoukee.

CORRESPONDENCE

87 **History and Diagnosis**
FAITH FITZGERALD, MD
DAVID R. GUTKNECHT, MD

87 **If Syncope, Think Long QT**
MARVIN L. AUERBACK, MD

87 **Correction**
DANIEL PIACQUADIO, MD

LESSONS FROM THE PRACTICE

88 **Quality Medicine**
ROBERT L. GOLDSTONE, MD

OTHER FEATURES

13 **Subscription Information**

20 **In Memoriam**

22 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

95 **Instructions for Authors**

97 **Classified Advertising**

106 **Western State Medical Associations' Meetings**

Poems: 40, 78, 82

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ABSTRACTS JULY 1992

(Geiman BJ, Smith AL: Dexamethasone and bacterial meningitis—A meta-analysis of randomized controlled trials. West J Med 1992 Jul; 157:27-31)

A meta-analysis of 5 randomized, controlled trials using dexamethasone as adjunctive therapy in the treatment of bacterial meningitis in children was done to assess the efficacy in reducing sequelae. A 6th study including both children and adults was analyzed separately. Results of the 5 pediatric studies indicated no significant difference in case-fatality rate between the placebo and dexamethasone groups. Significantly more neurologic sequelae were found in the placebo group during the period from discharge from hospital to 6 weeks after discharge (relative risk [RR] = 1.99, 95% confidence interval [CI] 1.13 to 3.53) and during the period beginning 6 months after discharge [RR = 3.90, 95% CI 1.72 to 8.85). The incidence of neurologic sequelae from 6 weeks to 6 months after discharge, though less with dexamethasone administration, did not reach statistical significance. The frequency of bilateral hearing loss was significantly greater in the placebo group (RR = 4.12, 95% CI 1.74 to 9.79), but unilateral loss was not statistically different in the two groups. Dexamethasone administration in addition to antimicrobial therapy appears to be effective in reducing neurologic sequelae and bilateral hearing loss associated with bacterial meningitis in children.

DEXAMETHASONE THERAPY
BACTERIAL MENINGITIS
ANTIMICROBIAL THERAPY
META-ANALYSIS

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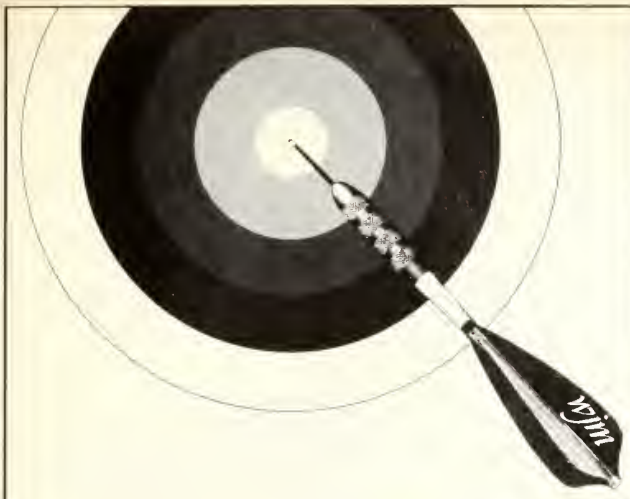

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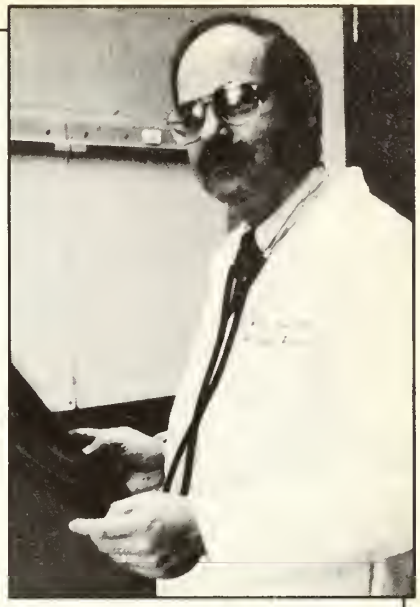

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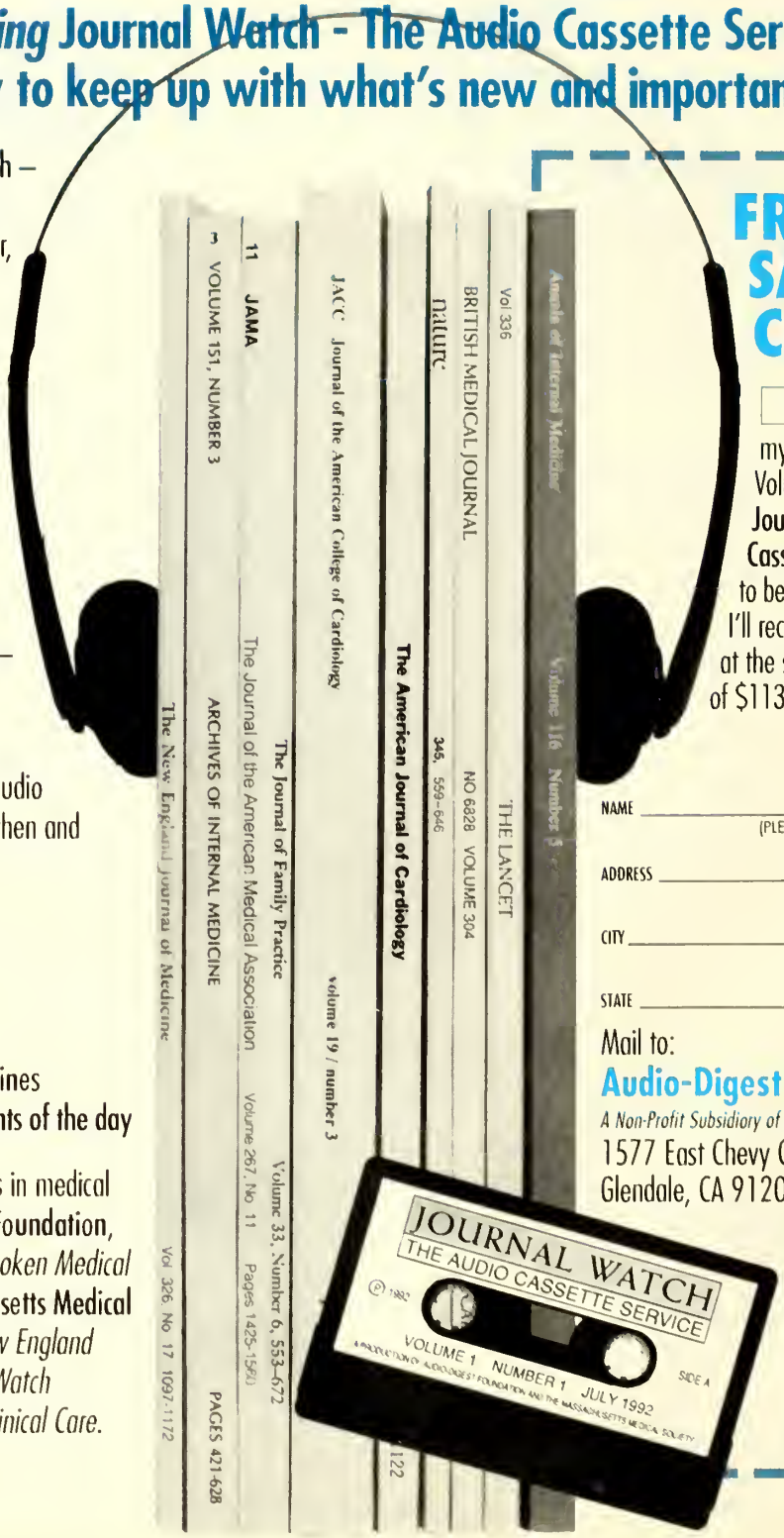

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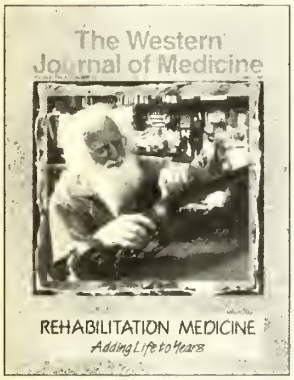

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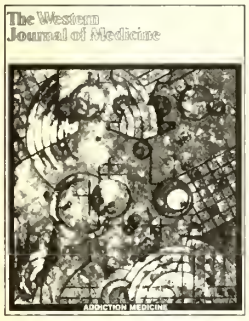

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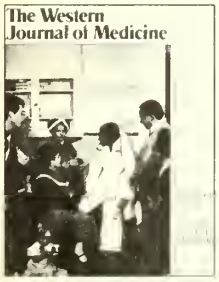

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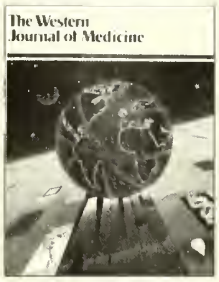

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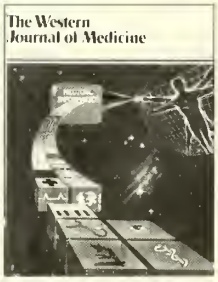

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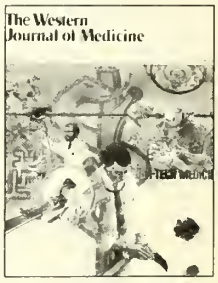

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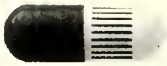

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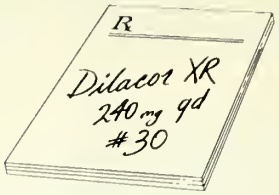

BRIEF SUMMARY

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant ß-adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with the histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Dilacor™ XR utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Dilacor™ XR.

Information for Patients. Dilacor™ XR capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor™ XR capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers or digitalis is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and an 18-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of impaired fertility was observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg patient) has resulted in embryo and fetal lethality. These studies have revealed, in one species or another, a propensity to cause abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights and pup survival, prolonged delivery and increased incidence of stillbirths.

There are no well-controlled studies in pregnant women; therefore, use diltiazem hydrochloride in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem hydrochloride is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies with other formulations, as well as with Dilacor™ XR. It should be recognized, however, that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The most common adverse events (frequency ≥1%) in placebo-controlled, clinical hypertension studies with Dilacor™ XR using daily doses up to 540 mg are listed in the table below with placebo-treated patients included for comparison.

MOST COMMON ADVERSE EVENTS
IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRIALS*

Adverse Events (COSTART Term)	Dilacor™ XR n=303 # pts (%)	Placebo n=87 # pts (%)
rhinitis	29 (9.6)	7 (8.0)
headache	27 (8.9)	12 (13.8)
pharyngitis	17 (5.6)	4 (4.6)
constipation	11 (3.6)	2 (2.3)
cough increase	9 (3.0)	2 (2.3)
flu syndrome	7 (2.3)	1 (1.1)
edema, peripheral	7 (2.3)	0 (0.0)
myalgia	7 (2.3)	0 (0.0)
diarrhea	6 (2.0)	0 (0.0)
vomiting	6 (2.0)	0 (0.0)
sinusitis	6 (2.0)	1 (1.1)
asthenia	5 (1.7)	0 (0.0)
pain, back	5 (1.7)	2 (2.3)
nausea	5 (1.7)	1 (1.1)
dyspepsia	4 (1.3)	0 (0.0)
vasodilatation	4 (1.3)	0 (0.0)
injury, accident	4 (1.3)	0 (0.0)
pain, abdominal	3 (1.0)	0 (0.0)
arthrosis	3 (1.0)	0 (0.0)
insomnia	3 (1.0)	0 (0.0)
dyspnea	3 (1.0)	0 (0.0)
rash	3 (1.0)	1 (1.1)
tinnitus	3 (1.0)	0 (0.0)

*Adverse events occurring in 1% or more of patients receiving Dilacor™ XR.

The following additional events (COSTART Terms), listed by body system, were reported infrequently in all subjects and hypertensive patients who received Dilacor™ XR (n=425): Cardiovascular: First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, palpitations, phlebitis, ECG abnormality, ST elevation; Nervous System: Vertigo, hypertonia, paresthesia, dizziness, somnolence; Digestive System: Dry mouth, anorexia, tooth disorder, eructation; Skin and Appendages: Sweating, urticaria, skin hypertrophy (nevus); Respiratory System: Epistaxis, bronchitis, respiratory disorder; Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhea, vaginitis, prostate disease; Metabolic and Nutritional Disorders: Gout, edema; Musculoskeletal System: Arthralgia, bursitis, bone pain; Hemic and Lymphatic Systems: Lymphadenopathy; Body as a Whole: Pain, unevaluable reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses: Amblyopia (blurred vision), ear pain.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. The administration of ipecac to induce vomiting and activated charcoal to reduce drug absorption have been advocated as initial means of intervention. In addition to gastric lavage, the following measures should also be considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation as well as the judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of diltiazem can vary over tenfold, which significantly limits their value in evaluating cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to hasten drug elimination. Overdoses with as much as 10.8 gm of oral diltiazem have been successfully treated using appropriate supportive care.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

Please see product circular for full prescribing information.

References:
1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.
2. *1992 Drug Topics® Red Book® Update.* Oradell, NJ, Medical Economics Co. Inc.; April, 1992.

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Please see adjacent page for brief summary of prescribing information.

In Memoriam

California Medical Association

Agcaoili, Felix, San Francisco. Died Feb 10, 1992, aged 66. Graduate of University of San Tomas, 1951. Licensed in California in 1960. Dr Agcaoili was a member of the San Francisco Medical Society.

Bacci, Orval J., San Jose. Died Apr 24, 1992, aged 71. Graduate of Creighton University, Omaha, Nebraska, 1947. Licensed in California in 1948. Dr Bacci was a member of the Santa Clara County Medical Association.

Bush, Robert C., Portola Valley. Died Mar 18, 1992, aged 71. Graduate of Harvard Medical School, Boston, Massachusetts, 1944. Licensed in California in 1950. Dr Bush was a member of the Santa Clara County Medical Association.

Chatton, Milton J., San Jose. Died Feb 17, 1992, aged 76. Graduate of University of California School of Medicine, 1943. Dr Chatton was a member of the Santa Clara County Medical Association.

Cochran, Frederick B., Jr, Oakland. Died Feb 1992, aged 40. Graduate of Albert Einstein College of Medicine, Bronx, New York, 1982. Dr Cochran was a member of the Alameda-Contra Costa Medical Association.

David, Charles B., Berkeley. Died Mar 25, 1992, aged 79. Graduate of Loyola University, Maywood, Illinois, 1940. Dr David was a member of the Alameda-Contra Costa Medical Association.

Gallion, Charles S., San Bernardino. Died Apr 19, 1992, aged 76. Graduate of College of Medical Evangelists, 1944. Licensed in California in 1944. Dr Gallion was a member of the San Bernardino County Medical Society.

Ginsberg, Julius E., Laguna Hills. Died Feb 8, 1992, aged 87. Graduate of Rush Medical College, Chicago, Illinois, 1932. Dr Ginsberg was a member of the Orange County Medical Association.

Hagan, Donald D., Laguna Beach. Died Mar 7, 1992, aged 46. Graduate of Louisiana State University, 1971. Dr Hagan was a member of the Orange County Medical Association.

Haruff, John J., Hollister. Died Apr 29, 1992, aged 84. Graduate of University of Colorado, Denver, 1932. Licensed in California in 1932. Dr Haruff was a member of the San Benito County Medical Society.

Hudson, Heber S., Visalia. Died Mar 22, 1992, aged 68. Graduate of University of Minnesota, 1951. Dr Hudson was a member of the Tulare County Medical Society.

Iseri, Lloyd T., Irvine. Died Feb 22, 1992, aged 74. Graduate of Wayne State University, Detroit, Michigan, 1944. Dr Iseri was a member of the Orange County Medical Association.

Lawther, Harry C., San Jose. Died Mar 31, 1992, aged 82. Graduate of University of Michigan, Ann Arbor, 1938. Licensed in California in 1946. Dr Lawther was a member of the Santa Clara County Medical Association.

Lubeck, Benjamin B., Kentfield. Died Apr 18, 1992, aged 49. Graduate of Temple University, Philadelphia, Pennsylvania, 1970. Dr Lubeck was a member of the Marin Medical Society.

Mayhew, Stephen H., La Jolla. Died Mar 1992, aged 48. Graduate of Johns Hopkins University, Baltimore, Maryland, 1968. Dr Mayhew was a member of the San Diego County Medical Society.

Morton, Mortimer E., Anaheim. Died Mar 1992, aged 73. Graduate of University of Southern California, Los Angeles, 1945. Dr Morton was a member of the Orange County Medical Association.

Noble, James H., Lynwood. Died Mar 10, 1992, aged 69. Graduate of University of California, San Francisco, School of Medicine, 1946. Licensed in California in 1946. Dr Noble was a member of the Los Angeles County Medical Association.

Nogle, Charles, Jr, San Francisco. Died Feb 18, 1992, aged 53. Graduate of State University of New York, 1964. Licensed in California in 1968. Dr Nogle was a member of the San Francisco Medical Society.

Pascoe, Richard L., San Diego. Died Feb 16, 1992, aged 68. Graduate of California College of Medicine, Irvine, 1962. Dr Pascoe was a member of the San Diego County Medical Society.

Peoples, Stuart A., Davis. Died Feb 14, 1992, aged 85. Graduate of University of California, 1934. Dr Peoples was a member of the Yolo County Medical Society.

Peterson, Robert H., Fresno. Died Mar 18, 1992, aged 67. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Peterson was a member of the Fresno-Madera Medical Society.

Poska, Ted A., Eureka. Died Mar 2, 1992, aged 83. Graduate of University of Illinois, Chicago, 1937. Dr Poska was a member of the Humboldt-Del Norte Medical Society.

Savage, Philip M., Jr, San Bernardino. Died Mar 12, 1992, aged 85. Graduate of University of Colorado College of Medicine, Denver, 1933. Licensed in California in 1934. Dr Savage was a member of the San Bernardino County Medical Society.

Schunke, Gustave B., Sacramento. Died Feb 20, 1992, aged 84. Graduate of Stanford University School of Medicine, Stanford, California, 1936. Licensed in California in 1936. Dr Schunke was a member of the Sacramento-El Dorado Medical Society.

Stansbury, John R., Ventura. Died Feb 23, 1992, aged 75. Graduate of University of Iowa College of Medicine, Iowa City, 1940. Dr Stansbury was a member of the Ventura County Medical Society.

Teague, Conrad B., Oakland. Died Mar 29, 1992, aged 67. Graduate of Johns Hopkins University, Baltimore, Maryland, 1953. Dr Teague was a member of the Alameda-Contra Costa Medical Association.

Weinberger, Herbert, Oakland. Died Jan 1992, aged 79. Graduate of University of Louisville, Kentucky, 1937. Dr Weinberger was a member of the Alameda-Contra Costa Medical Association.

Weizer, Ernest A., Watsonville. Died Mar 21, 1992, aged 83. Graduate of Loyola University, Maywood, Illinois, 1935. Dr Weizer was a member of the Santa Cruz County Medical Society.

Wilson, William M., Downey. Died Mar 27, 1992, aged 79. Graduate of University of Kansas, Lawrence, 1937. Licensed in California in 1939. Dr Wilson was a member of the Los Angeles County Medical Association.

Wynia, Frederick, Bakersfield. Died Feb 29, 1992, aged 80. Graduate of University of Oregon, Portland, 1941. Licensed in California in 1942. Dr Wynia was a member of the Kern County Medical Society.

New Mexico Medical Society

Badger, William E., Albuquerque/Hobbs. Died Mar 12, 1992, aged 83. Graduate of University of Michigan, Ann Arbor, 1934. Licensed in New Mexico in 1937. Dr Badger was a member of the Lea County Medical Society.

Rhodes, Gustave G., Albuquerque. Died Mar 24, 1992, aged 77. Graduate of University of Basel, Switzerland, 1939. Licensed in New Mexico in 1960. Dr Rhodes was a member of the Greater Albuquerque Medical Association.

Vergara, Luataro G., Albuquerque. Died Apr 3, 1992, aged 85. Graduate of University of Chile Medical School, 1933. Licensed in New Mexico in 1938. Dr Luataro was a member of the Greater Albuquerque Medical Association.

Waldman, Milton, Albuquerque. Died Mar 31, 1992, aged 80. Graduate of Lausanne University, 1941. Licensed in New Mexico in 1975. Dr Waldman was a member of the Greater Albuquerque Medical Association.

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983
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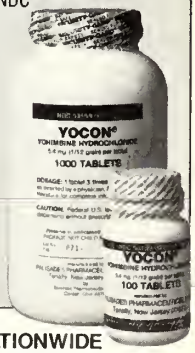

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August 17-21—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

August 19-23—**Wilderness Medicine: 1992.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Gene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

October 2-3—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Marina Del Rey. Fri-Sat. 15 hrs. Contact: Kathy Hester, (800) 451-7475.

October 10—**Emergency Medicine.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

October 19-23—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

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December 6-11—**Current Concepts in Emergency Care: 13th Annual Conference.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Jeannine Whidbee, 4192 Meridian Ave, Bellingham, WA 98226. (800) 544-9269.

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August 21-23—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Loews Coronado Bay Resort, Coronado Island, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 23-25—**7th Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $485. Contact: UCSF.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

October 15-18—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Maui Inter-Continental Hotel, Hawaii. Thurs-Sun. 16 hrs. $281-$375. Contact: UCLA Extension.

November 12-15—**CME/GOLF Meeting.** Nevada Academy of Family Physicians at Rio Hotel, Las Vegas. Thurs-Sun. 17 hrs. $225. Contact: Shone Ariotti, 895 Adams Blvd, Boulder City, NV 89005. (702) 293-0406.

GERIATRICS

November 16-18—**Geriatrics Update—1992.** Sharp Memorial Hospital at Loew's Coronado Bay Resort. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

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September 19—**AIDS.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, (916) 733-3883.

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Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

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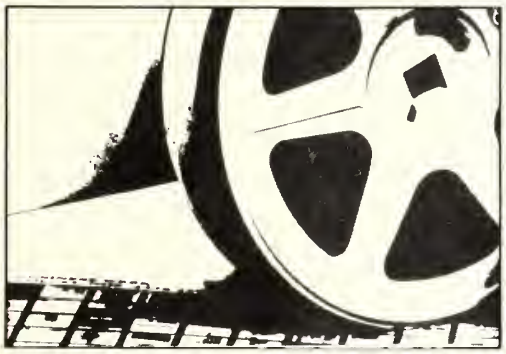

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References: 1. Data on file, Bristol-Myers Squibb Company. **2.** Cohn JB, Bowden CL, Fisher JG, Rodos JJ. Double-blind comparison of buspirone and chlorazepate in anxious outpatients with or without depressive symptoms. *Psychopathology* 1992;25:10-21. **3.** Feighner JP, Cohn JB. Analysis of individual symptoms in generalized anxiety—a pooled, multistudy, double-blind evaluation of buspirone. *Neuropsychobiology* 1989;21:124-130. **4.** Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26. **5.** Newton RE, Marunycz JD, Alderdice MT, Napoliello MJ. Review of the side-effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General*** – *Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients – Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions – Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations of SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility – No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects – Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers – Administration to nursing women should be avoided if clinically possible.

Pediatric Use – The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly – No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function – Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed*** – The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment – The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials – Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, contusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation – The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular* – frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System* – frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT* – frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine* – rare: galactorrhea, thyroid abnormality. *Gastrointestinal* – infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary* – infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal* – infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological* – infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory* – infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function* – infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin* – infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory* – infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous* – infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience – Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class*** – Not a controlled substance.

Physical and Psychological Dependence – Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms*** – At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdosage Treatment – General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

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Articles

Dexamethasone and Bacterial Meningitis
A Meta-analysis of Randomized Controlled Trials

BENJAMIN J. GEIMAN *and* ARNOLD L. SMITH, MD, *Seattle, Washington*

A meta-analysis of 5 randomized, controlled trials using dexamethasone as adjunctive therapy in the treatment of bacterial meningitis in children was done to assess the efficacy in reducing sequelae. A 6th study including both children and adults was analyzed separately. Results of the 5 pediatric studies indicated no significant difference in case-fatality rate between the placebo and dexamethasone groups. Significantly more neurologic sequelae were found in the placebo group during the period from discharge from hospital to 6 weeks after discharge (relative risk [RR] = 1.99, 95% confidence interval [CI] 1.13 to 3.53) and during the period beginning 6 months after discharge (RR = 3.90, 95% CI 1.72 to 8.85). The incidence of neurologic sequelae from 6 weeks to 6 months after discharge, though less with dexamethasone administration, did not reach statistical significance. The frequency of bilateral hearing loss was significantly greater in the placebo group (RR = 4.12, 95% CI 1.74 to 9.79), but unilateral loss was not statistically different in the two groups. Dexamethasone administration in addition to antimicrobial therapy appears to be effective in reducing neurologic sequelae and bilateral hearing loss associated with bacterial meningitis in children.

(Geiman BJ, Smith AL: Dexamethasone and bacterial meningitis—A meta-analysis of randomized controlled trials. West J Med 1992 Jul; 157:27-31)

Despite advances in antimicrobial therapy over the past 30 years, the incidence of sequelae from bacterial meningitis has remained high. Of the approximately 15,000 infants and children each year with bacterial meningitis in the United States, the case-fatality rate is about 2% to 5%.[1] Survivors have sequelae including neurologic problems and hearing loss in 20% or more cases.[2] Because of the high incidence of long-term sequelae, research has recently focused on the host's response to bacterial products instead of on antimicrobial therapy.[3] This line of reasoning is based primarily on the assumption that sequelae are the result of the host's response to the infection. Recent data implicate endotoxin from gram-negative bacteria and lipoteichoic acid from *Streptococcus pneumoniae*, released during antibiotic-induced lysis, as compounds that evoke the synthesis and release of several proinflammatory substances. These substances include prostaglandins, interleukin-1β, and tumor necrosis factor.[4,5]

The administration of anti-inflammatory glucocorticoids as an adjunct to antimicrobial therapy has been examined as a possible method of decreasing the host's response, thereby reducing the possibility of neurologic sequelae. In previous clinical trials, dexamethasone,[6-10] hydrocortisone,[11-13] hydrocortisone and prednisolone,[14,15] and methylprednisolone[15] have been administered as adjunctive therapy. A subjective analysis of data from these trials indicates that dexamethasone is a more effective adjunct than any of the other three glucocorticoids. A previous meta-analysis that included studies using all four regimens concluded that their pooled data were insufficient to support a beneficial effect of glucocorticoid therapy great enough to recommend its routine use.[16]

The question still to be answered is whether the use of dexamethasone as an adjunct to antimicrobial therapy is effective in reducing mortality, neurologic sequelae, and hearing loss associated with bacterial meningitis. To answer this question, a meta-analysis of all published, randomized, controlled trials assessing this therapy in children was done.

In areas in which controversy about the efficacy of a specific therapy exists, meta-analysis can be a useful alternative to traditional narrative reviews in reaching a conclusion. Pooling data from separate but related clinical trials results in greater power and therefore an increased chance of achieving statistical significance either favoring or refuting a specific intervention.

Methods

To obtain a comprehensive list of trials for use in this study, a MEDLINE search was conducted. MEDLINE was accessed for the period from January 1989, the year the previous meta-analysis[16] was published, through December 1991 to obtain studies published during that time. The decision to include a study was based entirely on the methods used and not on the outcome obtained. Criteria for inclusion were that the study was randomized and controlled and that it assessed the use of dexamethasone as adjunctive therapy in the treatment of bacterial meningitis in children.

Data were analyzed for four specific characteristics: case-fatality rate, neurologic sequelae, hearing loss, and cerebrospinal fluid (CSF) sterilization at 24 hours of therapy. Not all studies contained data for all characteristics of interest, so the specific studies used for each calculation are indicated. Analysis was performed using the Mantel-Haenszel test statistic for calculating relative risk (RR) and 95% confidence interval (CI).[17]

The results compare the risk within the placebo-controlled group to the risk within the dexamethasone treatment group. A relative risk of greater than 1 indicates an

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increased likelihood of the specific characteristic occurring in the placebo group and, therefore, a decreased risk within the dexamethasone treatment group. When the span of the 95% CI given did not include 1, the result was statistically significant.

Results

Five trials met the criteria for inclusion.[6-8,10] One article included two studies that differed with respect to the antimicrobial used,[7] and the two studies are considered separately in this analysis. An additional study by Girgis and associates met the criteria for inclusion except that both children and

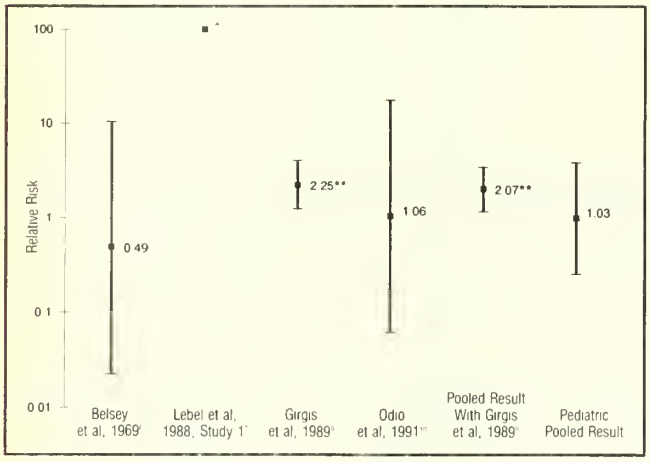

Figure 1.—The case-fatality rate is shown for individual and pooled data. No significant difference exists between groups in the pediatric pooled result. Pooling the data of Girgis and associates[9] shows a significantly increased case-fatality rate in the control group. ■ = relative risk, vertical bars = 95% confidence interval, ** = $P < .01$, and ■ ^ = calculated relative risk of infinity

adults were studied.[9] They also studied patients who, by a subjective determination of the duration of symptoms before admission and the state of consciousness on admission, were more ill as a group than those in the five pediatric studies.[9] Results are reported with and without this study.

All five pediatric studies were double blind and placebo controlled. The study by Girgis and co-workers was not placebo controlled or double blind.[9] To determine bacterial meningitis, all five pediatric studies and that of Girgis and associates used clinical signs and symptoms with confirmation by CSF culture or examination.[6-10] The five pediatric studies used bactericidal antimicrobials exclusively. Antimicrobial therapy in the study by Girgis and colleagues was not bactericidal for all organisms included in the study.[9] Dexamethasone dosage was 0.6 mg per kg per day in four studies[7,8,10] and 1.2 mg per m^2 of surface area per day in the fifth study.[6] Dosage in the trial by Girgis and associates was 16 mg per day in children younger than 12 years and 24 mg per day in patients older than 12.[9] The duration of dexamethasone administration was four days in all pediatric studies[6-8,10] and three days in the study by Girgis and co-workers.[9]

Case-Fatality Rate

The case-fatality rate within the dexamethasone and control groups was reported in all five pediatric studies[6-8,10] and by Girgis and colleagues.[9] One study included only patients surviving more than 18 hours after admission to hospital.[6] The number of patients, if any, who died during this time period was not indicated. Another study excluded a child from the analysis who was clinically brain dead on the second day of hospital stay.[8] Other than this exclusion, no deaths occurred within either group. Study 2 by Lebel and associates also reported no deaths.[7] Individually, relative risks within the three remaining pediatric studies[6,7,10] ranged from 0.49 to infinity, and none reached significance. The trial by Girgis and co-workers achieved statistical significance with dexamethasone therapy with a relative risk of 2.25 for the control group. Pooling the three pediatric studies[6,7,10] gave a relative risk for the placebo group of 1.03 (95% CI 0.27 to 3.89) when compared with the dexamethasone treatment group (Figure 1). Including the study by Girgis and associates[9] in the analysis resulted in a significantly greater case-fatality rate in the control group with a relative risk of 2.07 (95% CI 1.22 to 3.51). Adding the one patient from the placebo group who was excluded from the analysis by Lebel and co-workers[8] did not change the significance of either of these pooled results.

Neurologic Sequelae

The incidence of nonauditory neurologic sequelae was reported in all five pediatric studies[6-8,10] and in that of Girgis and associates.[9] One of the five studies reported sequelae that were present at follow-up less than six weeks after discharge,[6] one reported sequelae assessed between six weeks

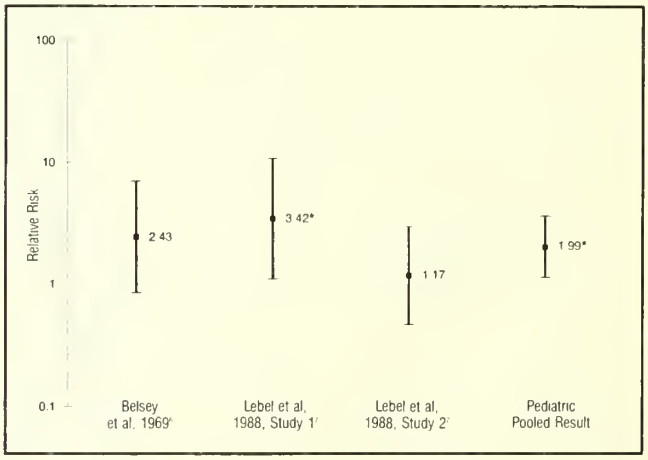

Figure 2.—The incidence of neurologic sequelae between discharge and less than 6 weeks after discharge is presented for individual and pooled data. The pediatric pooled result shows significantly increased neurologic sequelae in the placebo group. ■ = relative risk, vertical bars = 95% confidence interval, * = $P < .05$

and six months after discharge,[8] another reported sequelae assessed predominantly beyond six months after discharge,[10] and two reported the incidence of sequelae during all three time periods.[7] Girgis and colleagues reported sequelae that most closely fit the time period from six weeks to six months after discharge.[9]

The definition of nonauditory neurologic sequelae differed among the studies. One pediatric study defined "complications" rather than sequelae.[6] Nonauditory complications included coma, irritability and lethargy, paralysis, blindness, ataxia, altered behavior, decerebrate posturing, subdural effusion, convulsions, and abnormal reflexes. Patients in the study whose only complication fit the category of being irritable and lethargic were not, for this analysis, considered to have a neurologic sequela. Two pediatric studies included ataxia, hemiparesis, hypertonic extremities, and

cranial nerve abnormalities in their definition.[7] Another included hemiparesis, cranial nerve palsy, ataxia, speech impairment, and developmental impairment.[8] The fifth study did not explicitly define neurologic sequelae.[10] The only nonauditory neurologic sequela reported by Girgis and colleagues was paresis.[9]

Three pediatric studies reported sequelae during the period less than six weeks after discharge (Figure 2).[6,7] Relative risks within the individual studies ranged from 1.17 to 3.42. Study 1 by Lebel and associates was the only individual study to reach significance.[7] Pooling the three pediatric studies resulted in a significantly greater relative risk of neurologic sequelae in the placebo group of 1.99 (95% CI 1.13 to 3.53).[6,7]

Three pediatric studies and that of Girgis and colleagues reported neurologic sequelae during the period from six weeks to six months (Figure 3).[7-9] Relative risks for individual pediatric studies ranged from 1.21 to 1.97,[7,8] and none reached significance. Data from Girgis and co-workers also did not reach significance with a relative risk of 2.16.[9] The pooled relative risk of the three pediatric studies comparing the placebo group with the dexamethasone treatment group was not significant (RR = 1.47, 95% CI 0.74 to 2.90).[7,8] The result was also not significant when the data of Girgis and associates were included in the analysis with a relative risk for the control group of 1.51 (95% CI 0.85 to 2.68).

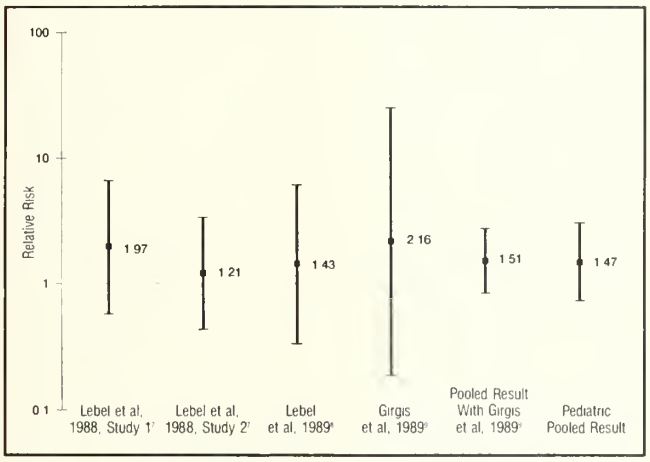

Figure 3.—The incidence of neurologic sequelae from 6 weeks to 6 months after discharge is shown for individual and pooled data. No significant difference between groups exists in the pediatric pooled result or when pooling with data of Girgis and co-workers.[9] ■ = relative risk, vertical bars = 95% confidence interval

Three pediatric studies reported neurologic sequelae for the period beginning six months after discharge (Figure 4).[7,10] One study included in this group reported sequelae during the period of "5 months to 25 months or more after discharge."[10] The relative risks of individual studies ranged from 3.51 to 4.18; the relative risk of Odio and colleagues' study reached significance.[10] Pooled data for these studies resulted in a significantly greater relative risk of sequelae in the placebo group (RR = 3.90, 95% CI 1.72 to 8.85).

Hearing Loss

The frequency of hearing loss was reported in four of the five pediatric studies.[7,8,10] One study noted that a child in the placebo group had "severe hearing loss" but did not define "hearing loss."[6] This study is not included in the analysis. Three of the five pediatric studies reported both unilateral and bilateral hearing loss[7,8]; one reported only bilateral loss.[10] Three studies assessed hearing-aid use among patients.[7,10] Girgis and co-workers assessed unilateral and bilateral hearing loss but not hearing-aid use.[9]

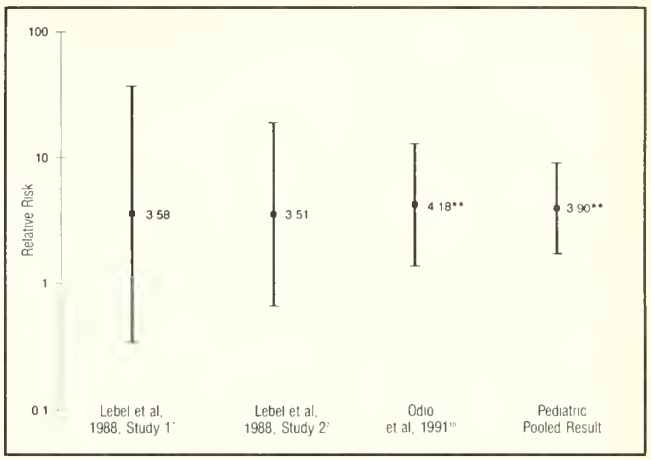

Figure 4.—The incidence of neurologic sequelae more than 6 months after discharge is shown for individual and pooled data. The pediatric pooled result shows significantly increased neurologic sequelae in the placebo group. ■ = relative risk, vertical bars = 95% confidence interval, ** = $P < .01$

Differences existed among the studies in the definition of hearing loss and in the method of assessing auditory acuity. Also, the time period in which hearing was evaluated varied. Girgis and associates did not evaluate hearing in patients younger than 4 years.[9] None of the other studies assessing this variable omitted study patients from evaluation because of age.

Relative risks for the four individual pediatric studies reporting bilateral hearing loss frequency ranged from 2.15 to 5.85[7,8,10]; study 1 of Lebel and co-workers reached significance.[7] Bilateral hearing loss frequency in the study by Girgis and colleagues was increased in control patients but was not significantly different from that in the dexamethasone group (RR = 2.78).[9] Pooling the four pediatric studies (Figure 5) resulted in a significantly increased relative risk in the placebo group of 4.12 (95% CI 1.74 to 9.79).[7,8,10] Including the study of Girgis and co-workers in the analysis also

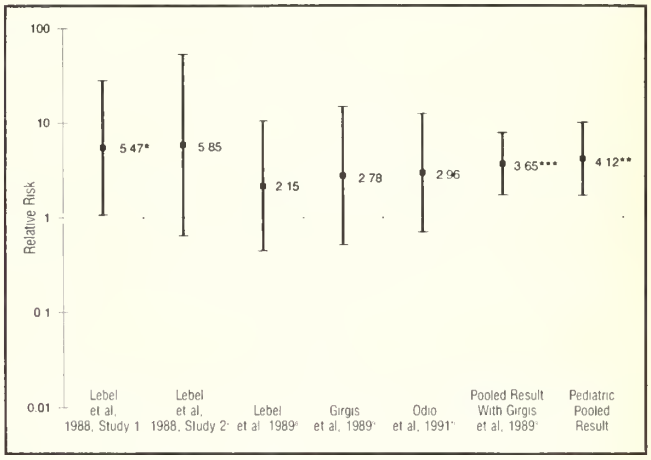

Figure 5.—The frequency of bilateral hearing loss is shown for individual and pooled data. The pediatric pooled result shows a significantly increased frequency of bilateral hearing loss in the placebo group. Also, pooling with the data of Girgis and colleagues shows a significantly increased frequency in the control group.[9] ■ = relative risk, vertical bars = 95% confidence interval, * = $P < .05$, ** = $P < .01$, *** = $P < .001$

resulted in a significantly greater relative risk for the control group (RR = 3.65, 95% CI 1.74 to 7.64).[9]

Data on unilateral hearing loss frequency could be obtained from three of the five pediatric studies by subtracting the frequency of bilateral hearing deficits from the numbers that included both unilateral and bilateral loss.[7,8] None of the individual pediatric studies reached statistical significance with relative risks ranging from 1.37 to 1.74. The data of Girgis and colleagues also did not reach significance with a relative risk of 1.09 for the control group.[9] When pooled, data on unilateral loss of hearing from the three pediatric studies (Figure 6) did not reach statistical significance with a

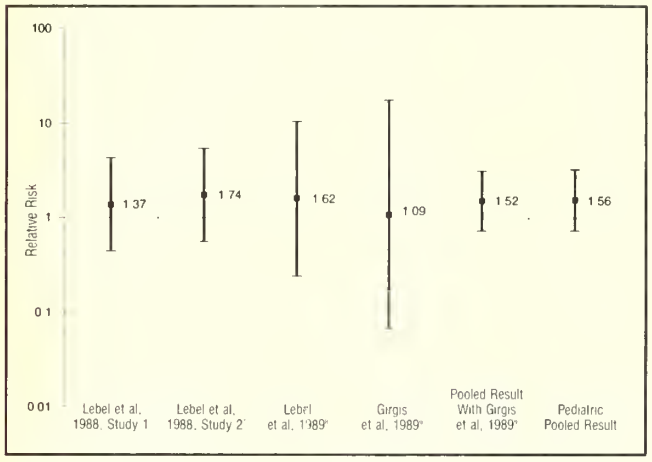

Figure 6.—The frequency of unilateral hearing loss is shown for individual and pooled data. No significant difference exists either between groups in the pediatric pooled result or when results are pooled with the data of Girgis and associates.[9] ■ = relative risk, vertical bars = 95% confidence interval

relative risk for the placebo group of 1.56 (95% CI 0.75 to 3.23).[7,8] Including the study of Girgis and associates in the analysis also did not result in a significant difference between the control and dexamethasone treatment groups (RR = 1.52, 95% CI 0.75 to 3.09).[9]

Three pediatric studies reported on hearing-aid use after meningitis.[7,10] Relative risks within individual studies ranged from 11.2 to infinity. Pooled results for the three studies yielded a significantly increased relative risk for the placebo group of 20.94 (95% CI 3.82 to 114.8) when compared with the dexamethasone group.[7,10]

Sterilization of Cerebrospinal Fluid

Sterilization of CSF at about 24 hours of therapy was assessed in all five pediatric studies.[6-8,10] Study 2 by Lebel and associates reported CSF sterilization both with and without the addition of cephalosporinase[7]; data with the addition of cephalosporinase are included in this analysis. None of the individual studies reached significance, and the relative risks varied from 0.94 to 1.37. When pooled, the five studies did not reach significance, with a relative risk for the placebo group of 1.18 (95% CI 0.57 to 2.43).[6-8,10]

Discussion

Several clinical trials reported within the past three years have indicated a beneficial effect of administering dexamethasone to patients with bacterial meningitis. The relatively small sample sizes in individual studies have made statistical significance hard to achieve. Pooling data from the five trials that assessed the administration of dexamethasone to children with bacterial meningitis helps to demonstrate the effectiveness of this therapy in reducing sequelae.

The methods used in this study differ from the meta-analysis reported by Havens and associates[16] in two ways. They pooled studies that used any of four glucocorticoids: methylprednisolone, hydrocortisone, hydrocortisone with prednisolone, or dexamethasone. In the study reported herein, analysis of one glucocorticoid, dexamethasone, reduces possible drug-specific bias. Also, Havens and co-workers included two studies in which bacteriostatic antimicrobials were administered.[16] This is important because of the concern about immunosuppression with dexamethasone administration and the failure to eliminate the bacteria if they are not killed by the antibiotic. The five pediatric studies included in this analysis treated patients only with bactericidal antibiotics. Delayed sterilization of CSF is associated with a greater frequency of sequelae.[18] Thus, therapy with a bacteriostatic antibiotic might be associated with more sequelae.

The case-fatality rate is the only variable for which the inclusion of the data of Girgis and colleagues affects the significance of the pooled result.[9] All five pediatric studies and that of Girgis and co-workers reported case-fatality data. The total number of fatalities in all five pediatric studies was six: three in the placebo group and three in the dexamethasone treatment group. Girgis and associates reported 62 deaths in the 429 patients studied.[9] It is evident that a pooled calculation of case-fatality rates that includes the data of Girgis and colleagues is going to reflect only their results.[9] Indeed, this is what occurred. The calculation of the case-fatality rate in the five pediatric studies was not significant, whereas including the fatality rate from the study by Girgis and co-workers resulted in significance.

The delay in treatment and the high case-fatality rate for patients in the study by Girgis and co-workers, as well as their inclusion of both children and adults, presents additional opportunities for bias when the data are pooled with the five pediatric studies. The main strength of the study of Girgis and colleagues seems to be in indicating the benefit of dexamethasone administration in a population with more advanced disease.[9] Indeed, the trial does show an impressive beneficial effect of adjunct therapy in this subset. Results are reported both with and without data from Girgis and associates, but the interpretation of pooled data is more accurate without them.

A temporal variation in statistical significance for neurologic sequelae occurred within this study. Data for two time periods achieved statistical significance, whereas those for the period from six weeks to six months after discharge did not. Slight differences in study populations are possible as a result of pooling different studies for the analysis of each time period. Also, differences in case definitions existed between studies. These two weaknesses help explain the difference in sequelae between time periods. It is unlikely that a change from nonsignificance in the six-week to six-month time period to significance in the period beginning six months after discharge was due to a change in the effect of the glucocorticoid therapy; instead, it was probably due to bias within the data.

The frequency of bilateral hearing loss was significantly different between the control and treatment groups and was less with dexamethasone administration; unilateral hearing loss was not significantly different. One possible explanation for this observation is that children who had bilateral loss of

hearing were more seriously ill as a group than those with unilateral loss. If patients with more severe disease had an untreated illness of a longer duration than the others, then the frequency of hearing loss was proportional to the duration the bacteria were present in CSF. Cefuroxime, administered in two trials,[7,8] has been associated with delayed sterilization of the CSF.[19] Thus, in these two studies, patients treated with cefuroxime may be similar to more severely ill patients in that bacteria were present in the CSF for a longer duration.[18,19] Dexamethasone administration appears to be of benefit in patients who have a longer duration of bacteria in CSF. Other analyses showed that when glucocorticoid administration and measures to control increased intracranial pressure were instituted, more severely ill children had reduced sequelae compared with no benefit in mildly ill children.[20]

Unfortunately, it was not possible to analyze sequelae by specific bacteria. Only one of the five pediatric studies reported neurologic complications or sequelae by agent.[6] None of the four pediatric studies assessing hearing loss frequency reported results by specific bacterium.[7,8,10] The ability to assess the incidence of sequelae caused by different agents would help in clarifying the benefit of dexamethasone use in each of these subsets of patients. Of 463 patients in the pediatric studies, however, 73% of cases of infection were due to *Haemophilus influenzae*. Thus, conclusions in this analysis do appear to apply to meningitis caused by that organism. This calculation includes 16 unmatched patients from one study who were not included in the analysis of other data characteristics.[6]

Gastrointestinal bleeding due to dexamethasone therapy is a possible adverse effect and was addressed in three studies.[7,8] In study 2 by Lebel and associates, two patients in the dexamethasone group experienced gastrointestinal bleeding.[7] No additional patient in the placebo or dexamethasone group in the three studies had gastrointestinal bleeding. An additional study calculated the incidence of guaiac-positive stools, which although not significant ($P = .055$) was lower in the dexamethasone than in the control group.[10] Despite the low incidence of overt bleeding reported in these studies, the prophylactic administration of a histamine-2 blocker may be prudent.

Meta-analysis, like any review of the literature, is subject to limitations. Problems can include variations in data quality between studies, reviewer sampling bias, and limitations in data retrieval from individual studies.[21] Reviewer sampling bias can result from the exclusive use of published results, the method used in this analysis, and the inclusion of only a subset of published articles addressing the specified therapeutic intervention. A danger of literature review specific for meta-analysis is that too much weight will be given to results using quantitative methods.[21]

Among these limitations, the exclusive use of published studies is of particular importance because of the possible influence of unpublished results on the statistical outcome of this work. This possibility is not a great concern. Regardless of the results, the likelihood of any well-done randomized, controlled trial of this therapy remaining unpublished seems small owing to the controversy that has long surrounded glucocorticoid therapy.

The first clinical trial assessing adjunctive dexamethasone therapy in the treatment of bacterial meningitis was published more than two decades ago with inconclusive results. In the past three years, several clinical trials suggested a beneficial effect in reducing the incidence of neurologic sequelae and bilateral hearing loss. Pooling data from five pediatric trials does support the efficacy of dexamethasone therapy with a minimum of short-term complications. The routine use of adjunctive dexamethasone therapy in bacterial meningitis, especially for severe cases due to *H influenzae*, seems warranted.

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Articles

Risk for AIDS in Multiethnic Neighborhoods in San Francisco, California

The Population-Based AMEN Study

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To examine the actual and potential spread of human immunodeficiency virus (HIV) from an acquired immunodeficiency syndrome (AIDS) epicenter to surrounding neighborhoods, we studied the prevalence of the viral infection and AIDS risk behaviors from 1988 to 1989 in a representative sample of unmarried whites, African Americans, and Hispanics living in San Francisco. We surveyed 1,770 single men and women aged 20 to 44 years (a 64% response rate) in a random household sample drawn from 3 neighborhoods of varying geographic and cultural proximity to the Castro District where the San Francisco epidemic began. Of 1,369 with blood tests, 69 (5%) had HIV antibodies; all but 5 of these reported either homosexual activity (32% HIV-positive; 95% confidence interval [CI] = 23%, 41%), injection drug use (5% HIV-positive; CI = 1%, 14%), or both (59% HIV-positive; CI 42%, 74%). Homosexual activity was more common among white men than among African-American or Hispanic men, but the proportion of those infected was similar in the 3 races. Both the prevalence of homosexually active men and the proportion infected were much lower in the 2 more outlying neighborhoods.

Risk behaviors in the past year for acquiring HIV heterosexually—sex with an HIV-infected person or homosexually active man or injection drug user, unprotected sexual intercourse with more than 4 partners, and (as a proxy) having a sexually transmitted disease—were assessed in 1,573 neighborhood residents who were themselves neither homosexually active men nor injection drug users. The prevalence of reporting at least 1 of these risk behaviors was 12% overall, and race-gender estimates ranged from 5% among Hispanic women to 21% among white women. We conclude that in San Francisco, infection with HIV is rare among people who are neither homosexually active nor injection drug users, but the potential for the spread of infection is substantial, as 12% of this group reported important risk behaviors for acquiring the virus heterosexually.

(Fullilove MT, Wiley J, Fullilove RE, et al: Risk for AIDS in multiethnic neighborhoods of San Francisco, California—The population-based AMEN study. West J Med 1992 Jul; 157:32-40)

The epidemic of the acquired immunodeficiency syndrome (AIDS) in San Francisco, California, has been marked by the rapid and virulent spread of infection among homosexually active men living in the Castro District.[1-3] Estimates derived from population-based seroprevalence studies of that neighborhood suggested that 49% of homosexually active men were infected with the virus by 1985. Massive and aggressive interventions developed by a coalition of community groups and public health officials[4,5] were effective in curbing further spread of the human immunodeficiency virus (HIV) among homosexually active men in that community.[6,7] Despite these successes, HIV infection has continued to spread in San Francisco, as evidenced by recent seroconversion among those participating in long-term cohort studies[8] and as suggested by the growing number of AIDS cases not attributable to male homosexual activity or injection drug use.[9]

The general patterns of such viral dissemination are well described. Over time, AIDS cases are reported from an ever-enlarging geographic area following patterns of hierarchic diffusion (spread from one population center to another distant one along travel routes) and spatial contagion (spread into areas contiguous with an epicenter).[10] The first reports of cases of AIDS, which came from such disparate places as New York City, Los Angeles, and San Francisco, illustrate hierarchic diffusion[11]; rates of infection among injection drug users in the northeastern United States, which vary inversely with distance from New York City, illustrate spatial contagion.[12] In local areas, HIV has spread within the sexual networks formed by gay men as well as in the sexual and

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
AMEN = AIDS in Multiethnic Neighborhoods
CDC = Centers for Disease Control
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus

needle-sharing networks formed by injection drug users. The sexual networks of those groups include people who are not themselves homosexually active men or injection drug users, a social connection that creates the potential for broad dissemination of the virus.

To study patterns of current and potential viral dissemination at the community level, we designed the AIDS in Multiethnic Neighborhoods (AMEN) Study. We selected ethnically mixed neighborhoods that were assumed to be vulnerable to the spread of HIV because of the close proximity to the Castro District and the high proportion of residents in treatment for injection drug use or gonorrhea. The diversity of the sample allowed us to examine the distribution of HIV risk behaviors and infection across groups defined by race, gender, and sexual orientation and to describe the sexual contact between those reporting the major high-risk behaviors—homosexually active men and injection drug users—and other members of the population residing in spatially contiguous areas. We used household probability sampling to provide a strong basis for generalizing the findings to similar high-risk communities in close geographic proximity to an AIDS epicenter.

Subjects and Methods

Selection of the Target Population

The selection of the target population was guided by three objectives: to identify a subpopulation of San Francisco residents who are, by objective indicators, at an increased risk of the transmission of HIV; to permit comparisons, with respect to HIV risk factors and HIV antibody status, among various subgroups of the city's population; and to allow efficient sampling of eligible study subjects by area probability sampling methods. These considerations led to the following definition of the target population: currently unmarried men and women, aged 20 to 44 years at initial contact, living in 16 census tracts of San Francisco. These tracts are characterized by high rates of reportable sexually transmitted diseases among women, by high rates of admission to drug detoxification programs, and by roughly equal numbers of African-American, white, and Hispanic residents.

The 16 tracts make up three distinct areas of the city: the Western Addition, the Mission District, and the Bayview-Hunter's Point District. According to the 1980 census, the populations of the Western Addition and the Bayview-Hunter's Point District were predominantly African American (71% and 87%, respectively), whereas the majority of the population of the Mission District, 51%, was Hispanic with a relatively small representation of African Americans (less than 5%). As shown in Figure 1, the Western Addition and Mission District lie along the northern and eastern borders of the Castro District, a district that was sampled in the San Francisco Men's Health Study because of its high prevalence of AIDS cases.

The population of the 16 tracts in 1980 was 77,200. Of this total, an estimated 27% (about 20,800) met the eligibility requirements for participation in the baseline survey. The distribution of the eligible population by race or ethnicity, based on ratio estimates from the 1980 US Census, was approximately 41% African American, 28% Hispanic, and 31% white and other racial groups.

Sampling Methods

The sample was designed so that each eligible person in the target population had the same probability of being selected—that is, the sample is "self-weighting." Within each of the 16 census tracts, blocks were chosen at random with probability proportional to the number of housing units in the block. Within each block, housing units were selected by

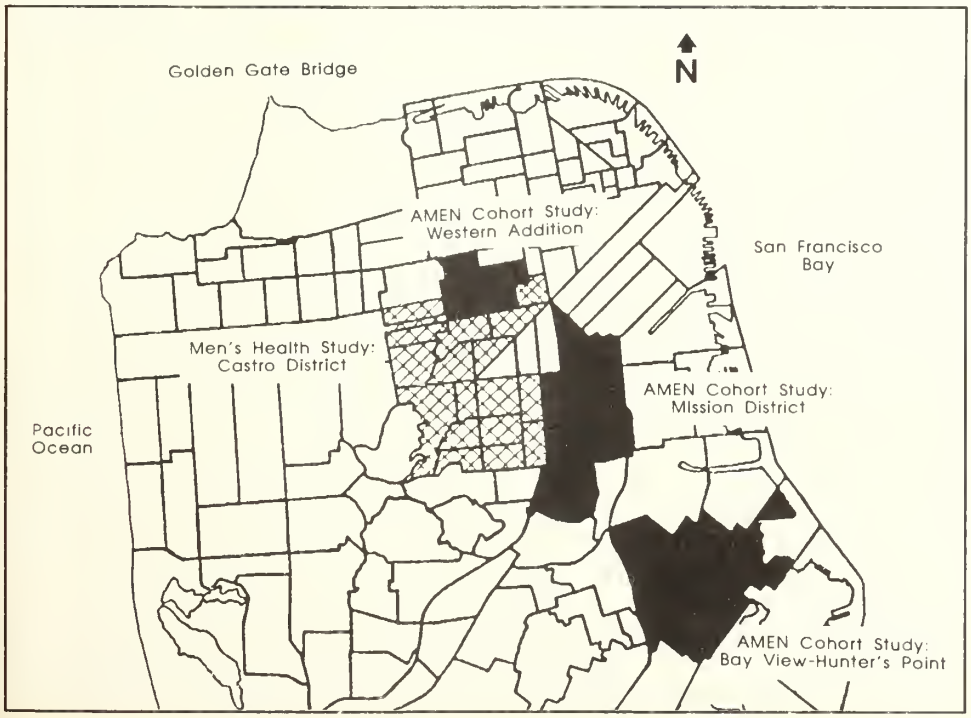

Figure 1.—The map of San Francisco shows the 3 neighborhoods surveyed in the AIDS in Multiethnic Neighborhoods (AMEN) Cohort Study **(solid black)** and the Castro District surveyed in the Men's Health Study (Winkelstein et al[7]) **(crosshatched).**

systematic random sampling. Each household in the target area has the same probability of falling in the sample (about 1 in 6.2). A total of 4,234 households were invited to participate in the baseline survey. Based on data collected in the fieldwork phase of the survey, 2,755 persons meeting the survey criteria were living in the selected households during the period of fieldwork.

Field Methods

Field operations were conducted by field-workers recruited and trained by the staff of the Survey Research Center of the University of California, Berkeley. In addition to training in administering interviews, each field-worker was certified to draw a specimen of blood by venipuncture. The protocol for contacts with selected households consisted of the following sequence of activities: An advance letter explaining the purpose of the survey was sent to each selected household before the first personal contact; at the initial home visit, a field-worker attempted to complete an enumeration interview to determine whether any persons eligible for participation were living in the household; if possible, the field-worker attempted to complete the baseline survey protocol with eligible members of the household during the initial home visit and to set up an appointment for a subsequent contact; and for each person identified as eligible in the enumeration phase, the complete home visit protocol was done. This consisted of

- Obtaining signed informed consent for participation;
- Administering a 45-minute face-to-face interview conducted in private and covering a wide range of HIV risk factors, psychosocial inventories, sociodemographic items, and information that would enable field-workers to recontact the participant for subsequent home visits;
- Collecting a specimen of blood by venipuncture in the home or in a nearby clinic;
- Telling each participant who donated blood how to obtain the results of the HIV antibody assay;
- Providing a $20 payment to compensate participants for their time.

All components of the home visit protocol, including the interview, were administered in Spanish when participants indicated a preference for Spanish.

Fieldwork for the baseline survey began in April 1988 and concluded in June 1989. Throughout this period, field-workers made repeated telephone calls to contact eligible persons who were not available at initial home visits and to reschedule home visits that had been missed or canceled. A special corps of highly trained interviewers attempted to complete the home visit protocol with eligible persons who had expressed a reluctance to participate in earlier contacts.

Serologic Tests

Serum was collected in 5-ml Vacutainer tubes, was refrigerated, and was delivered to the California State Viral and Rickettsial Disease Laboratory within 48 hours of collection. The laboratory assay employed a licensed commercial enzyme-linked immunosorbent assay (ELISA) kit from either Du Pont Medical Products or Genetics Systems following instructions on the package insert. Positive results were confirmed by a combination of a second ELISA from another manufacturer and an indirect immunofluorescence procedure developed in that laboratory.[13] Western blot and radioimmunoprecipitation testing were done on specimens considered discrepant by primary tests.

Instruments

The risk behaviors examined in this study do not carry an equivalent probability of HIV infection[14] but were chosen because they all increase the risk for HIV infection.[15-17] Risk behaviors were assessed by an interviewer reading the following questions:

- Male homosexual activity: "Over the last 12 months [have you had] sexual intercourse with another man . . . defined as follows: you put your penis in your partner's mouth or rectum, or your male partner puts his penis in your mouth or rectum?"
- Injection drug use: "Have you . . . injected any drugs into your veins or under your skin . . . within the last 12 months?"
- Having an HIV-infected sex partner: "[Has your partner of the past 12 months] ever had a test to detect the presence of the antibodies to the AIDS virus?" combined with "What did he or she say the result of his or her test was?"

TABLE 1.—*Recruitment for the AMEN Cohort Study and Participation of the Sample (n=2,755)*

Sex and Race Distribution	Enumerated, No.	Interviewed No.	Interviewed (%)
Men	**1,426**	**880**	**(62)**
White	586	397	(68)
African American	291	167	(57)
Hispanic	403	240	(60)
Other	112	76	(68)
Race unknown	34	0	(0)
Women	**1,329**	**890**	**(67)**
White	437	339	(78)
African American	445	289	(65)
Hispanic	323	195	(60)
Other	98	67	(68)
Race unknown	26	0	(0)
Total	2,755	1,770	(64)

AMEN = AIDS in Multiethnic Neighborhoods

- Having a homosexually active male sex partner (among women): "[Has your partner of the past 12 months] had sexual intercourse with another man at any time in the last 10 years?"
- Having a sex partner who uses injection drugs: "[Has your partner of the past 12 months] injected drugs into his or her veins or under his or her skin at any time in the last 10 years?"
- Having a sexually transmitted disease: "Have you . . . had any of the following diseases or conditions . . . during the last 12 months?" followed by individual questions about "syphilis," "gonorrhea or clap," "pelvic inflammatory disease," and "herpes sores in the genital or anal region";
- Having unprotected sex with more than four partners. questions about whether a condom was used "every time" for vaginal or rectal intercourse, asked individually for each of up to ten partners over the past 12 months.

The frequency of missing values for these risk behavior variables varied but was less than 4% in each case; these missing values were imputed to be zero. (The risk behaviors in Table 3 are based on similar items but refer to the longer

periods of time indicated in the footnote.) Near the end of the interview, race or ethnicity was assessed based on the respondent's choosing "which of the groups there best describes you" while looking at a page with seven printed categories. The subject's age was based on the birth date provided by the respondent, his or her education was established by the response to standard categories, and his or her income was determined by the respondent signifying the letter of the appropriate category from a list printed on a page.

Results

Demographic Characteristics of the Sample

A total of 4,232 households were contacted as part of the initial screening attempt to identify eligible respondents. Of those households, 95% were successfully enumerated. In all, 2,755 potential respondents were identified, of whom 1,770 (64%) agreed to be interviewed. Among whites, Hispanics, and those of other ethnic backgrounds, men slightly outnumbered women among those enumerated. Among African Americans, men were only 40% of those identified as possible participants.

Among those enumerated, women were more likely to participate in the survey than men (67% versus 62%, Table 1). Variation by race or ethnicity was also apparent: the response rate was 72% for whites, 62% for African Americans, 60% for Hispanics, and 68% for others. In considering gender and race or ethnicity together, we found the highest response rate (78%) among white women and the lowest among African-American men (57%). Examining response rates by age group and neighborhood (not shown in the table) revealed no significant differences.

The sample of 1,770 people interviewed comprised whites (41%), African Americans (26%), and Hispanics (25%); the remaining participants (8%) reported a diverse mixture of ethnic backgrounds (Table 2).[18] The sample was almost equally divided between men (880) and women (890). More than half of those surveyed reported an income of less than $18,000 per year. Two thirds had less education than a college degree, and half of these had a high school education or less.

The proportion of African Americans in our sample differed from that reported in the 1980 census. This shift was most pronounced in the Western Addition, where African Americans constituted 71% of single residents aged 20 to 44

TABLE 2.—*Demographic Characteristics and Human Immunodeficiency Virus (HIV) Antibody Seroprevalence of 1,770 Interviewees*

Characteristic	Total No. of Subjects	Serum Specimen Collected		HIV Antibodies		
		No.	(%)	No.	Point Estimate, %	95% CI, %*
Age, yr						
20-24	467	362	(78)	3	0.8	0.2-2.4
25-29	475	372	(78)	15	4.0	2.3-6.6
30-34	323	256	(79)	19	7.4	4.5-11.3
35-39	307	227	(74)	20	8.8	5.5-13.3
40-44	198	152	(77)	12	7.9	4.1-13.4
Total	1,770	1,369	(77)	69	5.0	3.9-6.3
Ethnicity and gender						
Men						
White	397	327	(82)	47	14.4	10.8-18.7
African American	167	117	(70)	7	6.0	2.4-11.9
Hispanic	240	180	(75)	8	4.4	1.9-8.6
Other	76	51	(67)	4	7.8	2.2-18.9
Total	880	675	(77)	66	9.8	7.6-12.3
Women						
White	339	282	(83)	1	0.4	0.0-2.0
African American	289	211	(73)	1	0.5	0.0-2.6
Hispanic	195	155	(80)	1	0.6	0.0-3.5
Other	67	46	(69)	0	0.0	0.0-6.3
Total	890	694	(78)	3	0.4	0.1-1.3
Income						
$0-5,999	414	328	(79)	4	1.2	0.3-3.1
$6,000-17,999	664	534	(80)	19	3.6	2.2-5.5
$18,000-29,999	442	335	(76)	28	8.4	5.6-11.9
$30,000-49,999	194	133	(69)	16	12.0	7.0-18.8
$50,000+	45	32	(71)	2	6.3	0.8-20.8
Total†	1,759	1,362	(77)	69	5.1	4.0-6.4
Education						
Less than high school	246	204	(83)	8	3.9	1.7-7.6
High school graduate	374	284	(76)	8	2.8	1.2-5.5
Some college	650	487	(75)	31	6.4	4.4-8.9
College degree	307	235	(77)	13	5.5	3.0-9.3
Postgraduate	181	149	(82)	9	6.0	2.8-11.2
Total†	1,758	1,359	(77)	69	5.1	4.0-6.4

*Approximate 2-sided 95% confidence intervals (CI) for proportions were calculated using the exact relationships among the binomial, β, and F distributions (from Johnson and Katz[18]). When the observed count was 0, the same method was used to calculate an approximate 1-sided 95% CI.

†Responses were missing for income in 11 cases and for education in 12 cases.

in the 1980 census but only 32% of the respondents in our study. African Americans constituted 87% of the residents of the Bayview-Hunter's Point District in the 1980 census and 5% of the residents of the Mission District, but in our study African Americans represented 77% of respondents from Bayview-Hunter's Point and 4% of the respondents from the Mission District.

Human Immunodeficiency Virus Infection

Of the 1,770 subjects in the AMEN cohort study, 1,369 (77%) agreed to have their blood tested for HIV antibodies. The two samples had similar distributions by race and gender (Table 2) and similar frequencies of risk behaviors. Homosexually active men were slightly less likely to be tested (Table 3), but the 60 persons who reported having injected drugs in the previous 12 months were significantly more likely to be tested than nonusers (90% versus 77%, $P < .05$), as were the 190 respondents who reported at least one lifetime episode of injection drug use (90% versus 76%, $P < .0001$).

Among those tested, 69 (5%) had antibodies (Table 2). Infection rates were much higher among men (n = 66) than among women (n = 3). Infection rates were higher among whites, among those reporting a higher annual income, and among those with more years of education, reflecting the demographic characteristics of homosexually active men in San Francisco. Of the 66 HIV-infected men, 62 reported one or both of the two major risk behaviors for HIV transmission (Table 3); 35% were both homosexually active and injection drug users, 55% were homosexually active only, and 5% were injection drug users only. Among the 23 infected men who were homosexually active injection drug users, 70% were white, 13% were African American, 13% were Hispanic, and 4% were in other racial groups. Among the 36 infected men who were homosexually active only, the distribution was 78%, 6%, 8%, and 8%, respectively. Among the three infected men who were injection drug users only, one was white, one was African American, and one was Hispanic.

The two HIV-infected men with other risk behaviors were both white: One had an HIV-infected female sex partner, and the other reported an injection drug-using female sex partner and sex with more than four partners without a condom in the past year. Of the two infected men who did not report risk behaviors, one was African American and one was Hispanic. Of the three infected women, two (one white and one Hispanic) reported injection drug use and one (an African-American woman) did not report any of the risk behaviors listed in the footnote to Table 3.

Table 3 provides population-based estimates for prevalence of infection in these risk groups. The HIV seroprevalence was 59.0% among men reporting both homosexual activity and injection drug use, 31.9% among those reporting homosexual activity, and 5.0% among those reporting injec-

TABLE 3.—*Human Immunodeficiency Virus (HIV) Antibody Seroprevalence in Study Group by Risk Group*

Risk Group*	Total No. of Subjects	Serum Specimen Collected		HIV Antibodies		
		No.	(%)	No.	Point Estimate, %	95% CI, %†
Men						
Homosexually active	157	113	(72)	36	31.9	23.4-41.3
Injection drug use (IDU)	70	60	(86)	3	5.0	1.0-13.9
Homosexually active and IDU	43	39	(91)	23	59.0	42.1-74.4
Other risk behavior	51	39	(77)	2	5.1	0.6-17.3
No identified risk	559	424	(76)	2	0.5	0.1-1.7
All men	880	675	(77)	66	9.8	7.6-12.3
Women						
IDU	77	71	(92)	2	2.8	0.3-9.8
Other risk behavior	80	68	(85)	0	0.0	0.0-4.3
No identified risk	733	555	(76)	1	0.2	0.0-1.0
All women	890	694	(78)	3	0.4	0.1-1.3

*Risk group classifications were based on reported injection drug use (ever, in whole life), homosexual activity (in past 10 years), and the following other risk behaviors: having a sex partner who is HIV infected (past 10 years), being a woman with a homosexually active male sex partner (past year), having a sex partner who injects drugs (past year), having had a sexually transmitted disease (past year), or having had sex with more than 4 partners without a condom (past year).

†Approximate 2-sided 95% confidence intervals (CI) for proportions were calculated using the exact relationships among the binomial, β, and F distributions (from Johnson and Katz[18]). When the observed count was 0, the same method was used to calculate an approximate 1-sided 95% CI.

TABLE 4.—*Distribution of High-Risk Behaviors for Human Immunodeficiency Virus (HIV) Infection in the Past Year in a Random Household Sample of Single Men and Women*

Risk Behavior in Past Year	Homosexually Active Men, Injection Drug Users, or Both (n=197), %	All Others (n=1,573), %	Total Subjects (n=1,770), %
Male homosexual activity (among men)	--	0	17
Injection drug use	--	0	3
Having an HIV-infected sex partner	13	0	1
Having a homosexually active male sex partner (among women)	15	2	2
Having a sex partner who injects drugs	27	5	7
Having a sexually transmitted disease	11	5	6
Having unprotected sex with more than 4 partners	6	3	4

TABLE 5.—*Distribution of Risk Behaviors by Race and Gender Among the Persons in This Study Who Are Not Homosexually Active Men or Injection Drug Users*

Risk Behavior in Past Year	White		African American		Hispanic		Other		Total
	Men (n=277), %	Women (n=325), %	Men (n=144), %	Women (n=285), %	Men (n=222), %	Women (n=189), %	Men (n=66), %	Women (n=65), %	(n=1,573), %
Having an HIV-infected sex partner	0	0	0	0	0	0	0	0	0
Having a homosexually active male sex partner (among women)	NA	4	NA	0	NA	1	NA	2	2
Having a sex partner who injects drugs	7	9	1	4	3	3	3	2	5
Having a sexually transmitted disease	5	9	6	6	2	3	0	3	5
Having unprotected sex with more than 4 partners	5	3	6	3	5	0	3	0	3
1 Risk behavior	12	18	11	8	8	4	6	6	10
More than 1 risk behavior	2	3	1	2	1	1	0	0	2

HIV = human immunodeficiency virus, NA = not applicable

TABLE 6.—*Distribution of Human Immunodeficiency Virus (HIV) Antibody Prevalence and of Risk Behaviors in Entire Study Population by Neighborhood*

Infection Status and Risk Behavior	Neighborhood			Total, %	P Value*
	Western Addition, %	Bayview-Hunter's Point, %	Mission District, %		
HIV infection, No.	**425**	**230**	**714**	**1,369**	
Prevalence of HIV antibodies	12	2	2	5	<.001
Risk behavior in past year, No.	**566**	**298**	**906**	**1,770**	
Male homosexual activity (among men)	28	10	11	17	<.001
Injection drug use	3	4	4	3	NS
Having an HIV-infected sex partner	3	0	1	2	<.001
Having a homosexually active male sex partner (among women)	5	0	2	2	<.001
Having a sex partner who injects drugs	8	6	7	7	NS
Having a sexually transmitted disease	8	5	4	6	<.02
Having unprotected sex with more than 4 partners	4	4	3	4	NS

NS = not significant

*P values represent χ^2 test for heterogeneity among neighborhoods.

tion drug use. The prevalence among men reporting other risk behaviors was 5.1%, and among those with no identified risk it was 0.5%; taking these two groups together yields a prevalence of 0.9% (95% confidence interval [CI] = 0.2% to 2.2%). For the women, the prevalence among injection drug users was 2.8%, among those with other risk behaviors it was 0%, and among those with no identified risk it was 0.2%; taking the last two groups together yields a prevalence of 0.2% (95% CI = 0% to 0.9%).

Risk Behaviors in the Past Year

Table 4 compares the 197 people who reported either male homosexual activity or injection drug use in the past year with the 1,573 who denied they participated in these behaviors (the number with at least one of these risk behaviors in the past year is smaller than the comparable number in Table 3 [347] because the latter includes behaviors extending over the past ten or more years). Homosexually active men and injection drug users reported higher rates of all the other risk behaviors than the rest of the population (Table 4). The latter group, however, a large majority comprised chiefly of heterosexually active people, reported substantial levels of risk. In these 1,573 men and women, the prevalence of reporting one or more of these risk behaviors in the past year was 12%.

In Table 5 we examine the race and gender distributions of these other risk behaviors among the 1,573 people who were neither homosexually active nor injection drug users. The prevalence of reporting one or more of the risk behaviors in the past year was lowest among women of Hispanic background (5%), intermediate among African-American women and men of all ethnic groups, and highest among white women (21%). The high levels of risk among white women were attributable to three main risk behaviors: having a sex partner who was an injection drug user (reported by 9%), reporting a recent history of sexually transmitted disease (9%), and having a homosexually active male sex partner (4%). For all three of these risk behaviors, the rates reported by white women exceeded those of all other race and gender subgroups.

Neighborhoods

The prevalence of HIV antibody varied among the three neighborhoods surveyed (Table 6). More than two thirds of those who were HIV-positive resided in the Western Addition, where the overall seroprevalence was 12%. The HIV seroprevalence rates were a sixth this level in Bayview-Hunter's Point (2%) and the Mission District (2%) ($P < .001$). The proportion of men reporting male homosexual activity showed the same pattern—28% in the Western Addition compared with 11% in the Mission District and 10% in the Bayview-Hunter's Point District ($P < .001$).

Although respondents in the Western Addition were significantly more likely to report an HIV-infected partner or a sexually transmitted disease ($P < .02$) and the women in this district were significantly more likely to report a homosexually active male sex partner ($P < .001$), the neighborhoods did not differ in the proportion of respondents reporting in-

TABLE 7.—*Racial Distribution of Homosexually Active Men and Human Immunodeficiency Virus (HIV) Infection in AMEN Cohort Study, by Neighborhood*

Race or Ethnicity	Western Addition			Mission District			Bayview-Hunter's Point			Total No.		
	Men, No.	Homosexually Active Men, No. (%)	HIV+ Homosexually Active Men, No. (%)	Men, No.	Homosexually Active Men, No. (%)	HIV+ Homosexually Active Men, No. (%)	Men, No.	Homosexually Active Men, No. (%)	HIV+ Homosexually Active Men, No. (%)	Men, No.	Homosexually Active Men, No. (%)	HIV+ Homosexually Active Men, No. (%)
White	157	55 (35)	30 (55)	152	23 (15)	7 (30)	18	6 (33)	1 (17)	327	84 (26)	38 (45)
African American	42	5 (12)	3 (60)	14	3 (21)	2 (67)	61	0 (0)	0 (0)	117	8 (7)	5 (63)
Hispanic	15	5 (33)	3 (60)	160	6 (4)	1 (17)	5	0 (0)	0 (0)	180	11 (6)	4 (36)
Other	12	2 (17)	2 (100)	30	3 (10)	1 (33)	9	2 (22)	0 (0)	51	7 (14)	3 (43)
Total*	226	67 (30)	38 (57)	356	35 (10)	11 (31)	93	8 (9)	1 (13)	675	110 (16)	50 (46)

AMEN = AIDS in Multiethnic Neighborhoods, HIV+ = human immunodeficiency virus-positive

*The total number of homosexually active men who are infected with HIV is 50 in this table, a smaller number than the 59 reported in Table 4 because homosexual activity is based on the past year in this table and on the past 10 years in Table 4. The percentages differ slightly from those in Table 6 because this table is restricted to those for whom HIV results are available.

jection drug use, having a sexual partner who was an injection drug user, or having unprotected sex with more than four partners.

There was significant variation in the rates of infection in homosexually active men reported in each neighborhood (Table 7); regardless of race, it was much higher in the Western Addition (57%) than in the Mission District (31%) or Bayview-Hunter's Point (13%, based on 1 case). The prevalence of homosexual activity was much higher among men who were white (26%) than among those who were African American (7%), Hispanic (6%), or of other racial backgrounds (14%). The different character of the neighborhoods is illustrated by the fact that even though most of the African-American men in our sample resided in the Bayview-Hunter's Point District, none of the eight homosexually active African-American men were Bayview residents. Although the numbers do not permit precise comparisons, the prevalence of HIV infection among homosexually active men was 63% in African-American men, 45% in white men, and 36% in Hispanic men.

Discussion

This is the first population-based study of HIV risk behaviors and HIV infection designed to sample approximately equal numbers of whites, African Americans, and Hispanics in urban neighborhoods. The study shows that HIV infection in San Francisco has occurred predominantly among homosexually active men, secondarily among injection drug users, and hardly at all in the rest of the population. Substantial numbers of people who are neither homosexually active men nor injection drug users have important HIV risk behaviors, however, the prevalence ranging from 5% to 21% across race-gender subgroups.

Current Levels of Infection

The levels of infection among homosexually active men who use injection drugs (59%), and among those who do not (32%), are comparable to those reported from the Centers for Disease Control (CDC) unblind study of similar men attending a sexually transmitted disease clinic (53% and 34%) but lower than those from the CDC blind study conducted at the same site (68% and 49%)[9] or from the San Francisco Men's Health Study in 1985 of a population-based sample in the Castro District (68% and 46%).[7] The levels of infection among injection drug users in our sample was 5%, which was similar to those in the CDC unblind study (3%) but lower than the rates in the CDC blind seroprevalence study (14%) or clinic studies (12%).[9]

The difference in HIV infection rates observed in the CDC studies between blind and unblind studies suggests a downward bias—that is, an avoidance of testing among those who are HIV-positive under conditions of confidential (as opposed to anonymous) testing. This suggests that our results, which are consistent with the estimates from the CDC unblind studies, provide a lower estimate for the actual seroprevalence in the neighborhoods examined. This interpretation is supported by findings from a household study in Dallas[19] that imputed that among those who refused to participate in the original survey but did respond to later requests and higher incentives, the HIV seroprevalence rate would be higher than it was in the group that responded initially.

Data from the CDC studies in San Francisco[9] suggest that the rate of HIV infection is 1% or less among those who are heterosexually active and do not report other risk behaviors. The levels of infection reported here—0.2% for women and 0.5% for men—are consistent with other studies. Because of the small numbers and many possible sources of error, including underreporting of risk behaviors, these point estimates of the level of infection may not represent the true population levels.

Potential for Spread of Infection

The risk behavior prevalences in this study are more important than the serologic findings in evaluating the potential for spread of the HIV epidemic into heterosexual populations. The overall prevalence of risk behaviors reported in the previous year among respondents who were not homosexually active men or injection drug users was 12%. Important risk behaviors are having a sex partner who used injection drugs (5%), having unprotected sex with more than four partners in the past year (3%), and women having a homosexually active male partner (2%). African Americans and Hispanics did not report higher levels of risk behaviors than whites. In fact, among people who were neither homosexually active nor injection drug users, white women (21%) and white men (14%) were the most likely to report one or more risk behaviors.

These behavioral data almost certainly underestimate true levels of risk behavior. Some respondents may underreport behaviors they perceive to be embarrassing,[20] and others may not be aware of their risk status. Several studies have indicated that some people who know they are HIV-positive

or who engage in high-risk behavior will conceal this information to establish a sexual relationship[21,22]; this could lead respondents in our sample to have inaccurate information about the risk behaviors or HIV status of their sexual partners. For these reasons, the observed 12% rate of engaging in HIV risk behaviors in the past year may underestimate the actual prevalence in the population. The data presented here, though indicating the relatively low infectivity of HIV through heterosexual intercourse in this population,[14] give us a basis for serious concern about future spread of the virus into populations that are currently unaffected.

Social Change and Geographic Concentration of Human Immunodeficiency Virus Infection

Geographic variation in the distribution of AIDS cases and of HIV infection has been described at all levels, from variation among countries (the Patterns I, II, and III described by the World Health Organization[23]) to variation among neighborhoods within a city (for example, high rates of infection in southwestern Belle Glade, Florida,[24] in the South Bronx section of New York City,[25] and in selected neighborhoods in San Francisco[26,27]). An important finding to emerge from studies of the geographic distribution of AIDS in the United States is the concentration of the disease in impoverished, inner-city communities[25,28] and in gay neighborhoods where many of the residents are homosexually active men.[7]

The dynamics of infection in neighborhoods have received little attention in studies of the epidemiology of AIDS. In one of the few studies of this issue, it has been argued that the virulent spread of infection in the South Bronx is related to massive social upheaval caused by the physical destruction of many acres of housing.[29,30] Neither the Castro District nor the Western Addition has suffered physical disintegration. On the contrary, both districts have experienced gentrification—a renewal and upgrading of neighborhood housing as more affluent whites replaced less affluent blacks—which is itself a manifestation of widespread social and physical change.

The Castro District was the first center of open gay life and culture. Gay men, through the Gay Liberation Movement, redefined their life-styles, and many chose to live in a setting conducive to their new choices.[31] Our study suggests that the gay community established in the Castro District has extended into an adjacent neighborhood, the Western Addition, and that this new community may have been created as part of a dramatic shift in the ethnic makeup of this area between 1980 and 1990. According to the census, the Western Addition, whose population was 70% African American and 19% white in the 1980 census, is no longer predominantly African American. The 1990 census indicates that African-American residents made up 51% of the neighborhood's population in 1990 and whites made up 32%.

We are unable to determine how this change in the community's ethnic composition may have changed other facets of community life. The Western Addition, however, had the largest proportion of homosexually active men in our study, the highest prevalence of HIV antibody among homosexually active men, and, as noted here, the greatest proportionate shift in ethnic distribution between 1980 and 1990. These findings suggest an association between a spatial diffusion of HIV infection and changes in the demographic composition of communities.

Conclusion

We have examined the prevalence of HIV infection and its antecedent risk behaviors in subgroups of the population defined by sexual orientation, ethnic group, and neighborhood. At present, the infection is most prevalent among homosexually active men living in the Western Addition, but it is also common in homosexually active men living elsewhere and in injection drug users. Infection is rare in the rest of the population, but given the prevalence of risk behaviors for acquiring HIV heterosexually, the potential is high for the future spread of infection into currently unaffected groups. Further, the model for HIV dissemination suggested by these data has important implications for other areas that are epicenters of the AIDS epidemic. Our data indicate that the spread of HIV infection will be slow, but the factors affecting the rate of spread are still incompletely understood and may change over time. Studies should also include an examination of patterns of spatial contagion and network diffusion of HIV infection in other epidemic epicenters such as New York City; Newark, New Jersey; and Miami, Florida.

It is also evident that prevention efforts need to be redoubled, particularly among persons who engage in risky behaviors and who fail to perceive (or who deny) the degree to which they are at risk. Even for behaviors that are associated with relatively low probabilities of acquiring HIV infection, any possibility of spread must lead us to encourage primary prevention through HIV antibody testing and safer sexual practices.[32-34]

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* * *

THIS SORROW WE ARE BOUND TO FACE

As if we are driving along the highway, a pleasant
straight-a-way, high-speed thoroughfare, and ahead
we sight it, the first stop-light in a thousand miles.

Its color, faintly visible, is green. Beside us,
a few vehicles pull into emergency lanes.
Just as we decide the light will remain in our favor,

as you relax your grip, the color changes to yellow.
Lined up, side-traffic is waiting to enter the intersection.
Playing the odds, relying on others, more cautious,

to look out for you, should you hold the gas pedal
to the floor? Trusting to luck, should you speed up,
risk colliding with those gunning engines, eager

to rush forward at the first sign of green? Or,
tapping the brake, should you pull toward the right,
continue in low gear? Swerve into a parking lane?

Stop? So with us, with this disease the doctors
have diagnosed: no side-roads, no turn-offs,
no way we can go but ahead. Already

the caution light is lit, we coast to a halt
as others, at full-speed, pull farther
and farther in front, as we, at a standstill, recede.

MARY BALAZS, PhD©
Lexington, Virginia

Health Care Use by Human Immunodeficiency Virus-Infected Students at a California Student Health Service

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Presented in part at the Seventh International Conference on AIDS, Florence, Italy, June 1991.

We report characteristics of 16 college students with human immunodeficiency virus (HIV) infection but without the acquired immunodeficiency syndrome who received care at a student health center at a major university in California. Sociodemographic and clinical data and medical expenditures were obtained retrospectively from medical charts and computerized billing records. All 16 students were men who had sex with men, and 3 had also used intravenous drugs. Dermatologic conditions, upper respiratory tract infections, gastrointestinal conditions, anemia, lymphadenopathy, sexually transmitted diseases, and ophthalmologic conditions were more frequent among HIV-infected students than among the general student population using the health center. On average, HIV-infected students visited the student health service about 3 times more often and incurred charges about 10 times higher than the general population of students visiting the health center. Student health centers, which have been at the forefront of developing strategies for HIV prevention, education, and counseling, must also develop treatment programs for HIV-infected students.

(Bennett CL, Chang H, Shlian D, Dawson JA, Edlin BR: Health care use by human immunodeficiency virus-infected students at a California student health service. West J Med 1992 Jul; 157:41-43)

Student health centers on college and university campuses are primary care providers that will be increasingly involved in early intervention for human immunodeficiency virus (HIV) disease. These centers are potentially responsible for providing health care for the 13 million undergraduate and graduate students in the United States. As many as 35,000 college students may be infected with HIV.[1,2] College students engage in behavior that may place them at risk for HIV infection[3,4]; in addition, alcohol and substance abuse may impair judgment about sexual risk taking. High rates of sexually transmitted diseases among college students[5-9] are evidence of this behavior. Although prevention, screening, and education programs have been designed for student health centers,[10] little is known about the clinical care required by HIV-infected college students. To investigate clinical characteristics and costs of care of HIV-infected college students, most of whom would not be expected to have overt acquired immunodeficiency syndrome (AIDS),[11] we collected data on HIV-infected college students without AIDS who received medical care at a student health service.

Patients and Methods

Student Population

Data were collected from the student health center at a large university in southern California. More than 30,000 students attend the university, two thirds of whom are undergraduates. The center provides acute and chronic primary and subspecialty care, health promotion, and prevention services. In 1989, more than 12,000 students visited the center and 50,000 patient visits (exclusive of psychiatric visits) were recorded (for an average of about four visits per student). Two thirds of the visits were by undergraduates and about 60% were by women. According to internal audits by the student health center, students in the general student body who used the student health center averaged about four visits per year and $200 in medical charges (H.C.).

All undergraduate and graduate students who had documented HIV infection but not AIDS and who received medical care at the student health center between January 1, 1987, and December 31, 1990, were included in this report. Students were identified for inclusion by searching computerized health center records for HIV-related International Classification of Diseases, ninth revision, codes (codes 042 to 044).[12] One student who had AIDS when first seen was excluded.

Data Collection and Analysis

Data were collected from the medical records and computerized billing records of the student health center using a previously described instrument.[13] Sociodemographic (age, race, sex, insurance status, risk group, and year of college education) and clinical (diagnoses for each visit, history of sexually transmitted diseases, AIDS-defining conditions, laboratory tests, and HIV-related pharmaceutical use) data were abstracted by a study physician for the most recent 12-month period for the students who did not progress to AIDS

From the Rand Corporation, Santa Monica, California, the Center for Health Policy Research and Education and the Division of Hematology/Oncology, Duke University and the Durham Veterans Affairs Medical Center, Durham, North Carolina (Dr Bennett); the University of California, Los Angeles, School of Public Health (Dr Chang); the UCLA School of Medicine (Drs Shlian and Dawson); and the Centers for Disease Control, Public Health Service, US Department of Health and Human Services, Atlanta, Georgia (Dr Edlin).

This work was supported in part by a University of California Statewide Task Force grant No. 90RCC86CA to the UCLA Clinical Research Center. Dr Bennett is a recipient of a Career Development Award from the Department of Health Services Research of the United States Department of Veterans Affairs.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

and for the 12-month period before the diagnosis of AIDS for the three students who progressed to AIDS.

We obtained medical charges from the university cashier's fee-for-service handbook. Costs for mental health services were provided by the student psychology service. For four students who had been followed longer than 6 months but shorter than 12 months, outpatient services were imputed to an annualized amount. Three students with private health insurance also received care from private physicians; these services were not included in this study. Inpatient charges were not included in these analyses because no patient required inpatient care during the 12-month period for data collection. The data for the use of medical resources in this study represent charges, not the costs of producing the services, unless otherwise indicated.

TABLE 1.—*Diagnoses at Student Health Center Visits of HIV-Infected Students Without AIDS and All Students*

	HIV-Infected Students Without AIDS			All Students
Diagnostic Category	*Students, No. (n=16)*	*Visits, No. (%)* (n=183)*		*Visits, % (n=49,930)*
Dermatologic	12	42	(23)	12
Upper respiratory tract	11	36	(20)	20
Gastrointestinal	9	33	(18)	4
Anemia	3	15	(8)	<1
Lymph nodes	4	13	(7)	--
Eye problems	9	12	(7)	2
Sexually transmitted disease	5	12	(7)	2
Counseling	6	7	(4)	2
Fatigue	5	7	(4)	--
Musculoskeletal	5	6	(3)	9
Anxiety	3	6	(3)	--
Fevers	3	5	(3)	--
Routine care	2	4	(2)	--
Genitourinary	2	4	(2)	2
Ear, nose, throat	1	4	(2)	--
Pain	1	1	(1)	2
Allergies	1	1	(1)	2

AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus

*Students may have had more than 1 diagnosis at each visit.

Approval was obtained from the human subjects committee before initiating the study.

Results

Sixteen HIV-infected students received care from the student health service between 1987 and 1990. All 16 were men; their median age was 30 years (range, 21 to 40 years). Eleven were white, 3 were Hispanic, 1 was African American, and 1 was Native American. Six were undergraduates; ten were graduate or professional students. Eleven students had private health insurance, two students had no health insurance, and for three students health insurance information was unavailable. All of the students visited the student health center with questions regarding the possibility of HIV infection, and all 16 had confirmatory antibody testing. All 16 students were men who had sex with men, and 3 also had injected drugs. *Pneumocystis carinii* pneumonia developed in three students, who elected to obtain medical care elsewhere thereafter. The $CD4^+$ lymphocyte counts were recorded for 12 of the students: 1 had less than 200×10^6 per liter, 5 had between 200 and 500×10^6 per liter, and 6 had greater than 500×10^6 per liter.

Data about care provided to the 16 students were collected for 180 student months (range, 9 to 12 months per student). The students visited the student health center an average of 12.5 times (range, 1 to 22 visits) (Table 1). Only two students had fewer than five visits in the 12-month period. The most common diagnoses were dermatologic conditions, upper respiratory tract infections, gastrointestinal conditions, anemia, lymphadenopathy, sexually transmitted diseases, and ophthalmologic conditions. All of these problems were noted at a higher frequency among HIV-infected students than among the general student body (Table 1). Acute or chronic sexually transmitted diseases were frequent: one student had condylomata acuminata, two students had molluscum contagiosum, one student had gonorrhea, one student had chlamydial infection, and one student had herpes simplex infection. Seven students received zidovudine, and two received aerosol pentamidine.

The mean (±) annual health care charge was $2,125 (± $1,150), which is about ten times the mean annual charge for a student in the general student body. Of these charges, 45% were for office visits, 39% were for laboratory tests, 7% were for radiographs, and 9% were for mental health services. Although pharmaceutical charges were not included in these analyses, eight students were receiving zidovudine, aerosolized pentamidine, or both.

Discussion

We describe health care provided to HIV-infected students at a student health center at a major university in southern California. Sixteen HIV-infected students, three of whom progressed to AIDS, received care at the student health center. The 16 students had an incidence of various medical problems common in HIV-infected persons[14] that was higher than in the general student population. The HIV-infected students visited the student health service about three times as frequently and incurred charges about ten times as high as students in the general student body.

The number of students who received care for HIV infection at this health center was small. Distributions according to age, sex, and race were similar, however, to those of HIV-infected college students reported in large cross-sectional seroprevalence studies.[1,2]

Interventions targeted at specific high-risk groups have been advocated as an efficient strategy for HIV prevention.[15,16] Although injection drug use is thought to be rare on college campuses,[2,4] it is likely that, because of their high risk of HIV infection, students with a history of injecting drugs are overrepresented among HIV-infected students. Our data suggest that this group may be an important target for intervention at some colleges.

Our data also suggest that medical care and counseling for HIV-infected students may require considerable resources, even for a small number of students. In this study HIV-infected students had a mean annual charge of $2,125, exclusive of pharmaceutical costs. This figure is similar to estimates based on theoretic models.[16,17] In addition, some HIV-infected students were receiving zidovudine therapy,

which typically represents an additional expense of $2,400 per person.[18]

Student health centers need programs to implement HIV education, prevention, counseling, and testing.[10] Our data suggest that student health services in some colleges should also expect to devote considerable resources to the care of HIV-infected students.

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Articles

Factors Influencing Family Physicians to Continue Providing Obstetric Care

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To determine the reasons some family physicians continue to practice obstetrics when most of their colleagues do not, we surveyed family physicians in 26 counties of northern California whose practices include obstetrics and those who have recently discontinued it. In all, 70% of family physicians practicing obstetrics cited enjoying it as a reason for continuing this practice. Over a third of family physicians practicing obstetrics thought that obstetric practice was a responsibility to the community. Only 1 in 6 reported obstetrics to be important in terms of financial implications. Despite this, family physicians practicing obstetrics had a mean gross income derived from obstetric practice of $30,000 above the cost of their total malpractice premium. In contrast, a comparison group of family physicians who had recently discontinued obstetrics cited malpractice insurance costs most frequently as the reason for discontinuing it. Nearly 40% of these physicians indicated that they would be willing to return to obstetrics if circumstances were to change substantially. The most frequently cited change necessary for these physicians to return to obstetrics was a reduction in malpractice insurance rates.

(Nesbitt TS, Kahn NB, Tanji JL, Scherger JE: Factors influencing family physicians to continue providing obstetric care. West J Med 1992 Jul; 157:44-47)

Family physicians are trained to care for individual patients and families throughout the life cycle. A central element of health care for families involves pregnancy and the birth process. There is much evidence that family physicians provide high-quality perinatal care and have qualities that obstetric patients value highly.[1-3] Despite this evidence, most family physicians no longer provide perinatal services in their practices.[4]

In areas where obstetric services are readily available, family physicians may have less difficulty choosing not to provide such services. In rural areas, where the majority of obstetric providers are family physicians and where there has been an overall loss of 20% of obstetric providers in the past five years, this decision is more difficult.[5] Rural America has disproportionately high rates of infant mortality, and there is evidence that local obstetric care is a critical variable in ensuring optimal birth outcomes.[6,7] In addition, with access to obstetric care in nonrural areas of the United States an issue of increasing concern, we cannot ignore the potential source of care represented in the more than 2,400 family practice residents in the United States each year who graduate with mandatory training in obstetrics.[8] Also, more than 30,000 practicing family physicians who report including perinatal care in their practices at some time in their careers currently do not.[4,9] It is also estimated that about 12% of obstetricians have discontinued offering obstetric care in the past several years.[10] During the past two years in the 26 northern California inland counties, there has been a 13% attrition of the obstetric providers overall.[11] With regard to new family physicians, only 32% of graduates of the six nonmilitary family practice residency programs in this same area were including obstetrics in their practices in 1988, down from 54% in 1980.[12]

Family physicians have traditionally cited malpractice issues as reasons for discontinuing obstetrics; however, life-style and other issues are now also being given as concerns.[13,14] For family practice residents, it appears that the lack of role models and misconceptions about the cost of malpractice insurance contribute to their decisions not to include obstetrics in their practices on graduation.[15,16]

Unfortunately, little has been written concerning the benefits of including obstetrics in family practice, particularly regarding the motivations for family physicians in their attitudes and the economic implications.[17] This study was undertaken to determine the reasons family physicians have chosen to continue including obstetrics in their practices when most of their colleagues have discontinued this service. In addition, we describe notable characteristics of these physicians, comparing them with their counterparts who have recently discontinued obstetrics, and the economic implications of continuing to include it in their practices.

Methods and Study Group

The study area includes the 26 noncoastal northern California counties and represents about 30% of the land mass of California (Figure 1). The economy in this region is primarily agriculture and forest products. There are three communities in the area with a population over 100,000, and the total population is about 3 million. The names and addresses of 748 family physicians practicing in this area were obtained from records from the California Academy of Family Physicians. The list is maintained by the academy, is updated

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annually, and includes members and nonmembers. A postcard survey was sent to the complete group to determine whether the physicians were currently practicing obstetrics, had discontinued obstetrics in the past four years, had provided obstetrics before four years ago, or had never included obstetrics as a part of their practices. The response rate from the postcard survey was 87%. Through telephone inquiries with area hospitals, we identified an additional ten family physicians with current or recent obstetric experience. Four of these physicians were practicing obstetrics; six had recently discontinued. A more detailed survey was sent to physicians currently practicing obstetrics and to those who had recently quit. Those physicians who identified themselves as currently practicing obstetrics but who did not respond to the survey were contacted by phone. Physicians were eliminated from the study if they were still in training, primarily teaching in a residency program, or in military service (Figure 2).

Both groups of physicians were asked about the number of deliveries they had performed during their training, their age, practice type, number of years in practice, malpractice

Figure 1.—The geographic area of the study includes 26 inland northern California counties and excludes western Solano County.

insurance carrier, and the percentage of their practice covered under Medicaid (Medi-Cal in California). Physicians practicing obstetrics were asked how many deliveries they had performed in the previous year and to estimate their gross income generated from the obstetric portion of their practice and the cost of their total professional liability insurance premiums for the previous year.

Using an open-ended format to minimize bias or limit the number of responses, we also asked family physicians currently practicing obstetrics why they were continuing. The responses to this question were reviewed and coded independently by three reviewers and grouped into categories. When more than one response was given, each was included in its appropriate category. Each comment was placed in one category only. If several comments by a physician were considered to apply only to a single category, then those comments were credited as a single response.

For family physicians who had recently discontinued obstetrics, a closed format based on previous studies was used to survey reasons for discontinuing this service.[9,13,14] There was also space provided in the question for an open-ended response. These physicians were also asked whether they would return to obstetrics under certain conditions. Those responding positively to this question were asked about what specifically would need to change for them to reenter obstetrics.

A variety of statistical methods were used in the analysis of the data. For continuous data where the distribution was

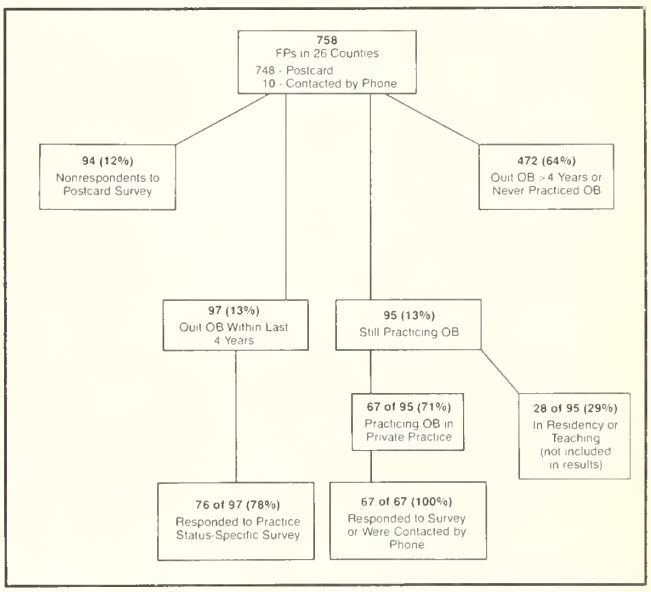

Figure 2.—The breakdown of family physicians (FPs) is shown for the study area by obstetric (OB) practice status.

normal, Student's *t* test was used. For nonparametric data (number of deliveries during training), a Mann-Whitney test was used to assess significance. In the analysis of the number of physicians from each group practicing in cities with a populace of more than 50,000, an odds ratio was calculated with a 95% confidence interval (CI).

Results

We found 95 family physicians were currently practicing obstetrics in the 26 inland counties of northern California. Of these, 28 physicians who were practicing within a residency program or in the military were excluded, leaving 67 obstetrically active family physicians. We identified by the postcard mailing that 97 family physicians from the same geographic area had stopped the obstetric portion of their practice within the previous four years. Of the 97, 76 (78%) responded to the questionnaire and constituted the comparison group for the study.

Although statistically significant, there was little difference in the mean age or years in practice between the two groups of physicians (Table 1). They were also remarkably similar in their carriers of malpractice insurance. There were minor differences in the type of practice. Many more physicians continuing obstetrics were in partnerships; a greater number of those who discontinued were in group practices,

health maintenance organizations, or other practice situations such as urgent care clinics or emergency medicine. Also, those who had discontinued obstetrics were much more likely to practice in a community of 50,000 or more (odds ratio 2.56 [95% CI 1.26 to 5.25]). In addition, for those still practicing obstetrics, the mean estimated portion of their practice that was on Medicaid was 27% overall and 49% in their obstetric practices. This compares with 17% currently for the overall practice for those who have discontinued obstetrics. These physicians estimated the Medicaid portion of their previous obstetric practice was 29%. There was no significance in the number of deliveries done in training between the group that continued (218 ± 157) and the group that stopped (180 ± 191) delivering babies. The group that continued obstetrics delivered an average of 53 (±48) babies in the previous year.

TABLE 1.—*Demographic Data of Family Practice Physicians in Northern California in Our Survey*

Physician Data	*Continuing Obstetrics n=67*	*Discontinued Obstetrics n=76*	*P Value**
Age, yr	41±10	44±15	<.05
Years in practice, No.	10±7	13±11	<.05
Insurer, %			
Norcal	52	56	
Doctors	27	17	
Other	6	2	
None	14	6	
Practice type, %			
Group	40	32	
Partnership	24	9	
Solo	23	23	
Multispecialty	10	17	
Health maintenance organization	0	4	
Other	3	14	

*Student's *t* test.

A major focus of this study was to determine why these family physicians continue to practice obstetrics despite all the obstacles noted throughout the literature. Physicians were asked why they plan to continue obstetrics in their practices; 63 physicians answered this question, and there was an average of two different reasons given per physician. The most common answer related to personal satisfaction, with 45 physicians (more than 70%) stating that they enjoyed the practice of obstetrics (Table 2). Over a third of the physicians felt that obstetrics was their responsibility to the community. Approximately a quarter of the physicians saw obstetrics as a practice enhancer in that they thought it helped build the practice or keep certain characteristics that are desired in their practice. About a fourth considered obstetrics an important part of their specialty. About one in six physicians reported that it was important in terms of income.

Of the 76 physicians in the group that had discontinued obstetrics, 73 responded to the question as to why they discontinued this service (multiple responses were allowed). Of these physicians, 52 (71%) cited the cost of liability premiums as a reason for discontinuing obstetric practice, 32 (44%) gave the fear of being sued as a reason, 21 (29%) indicated insufficient reimbursement, and 17 (23%) physicians indicated that life-style issues were an important concern. Administrative problems, patient noncompliance, and age or retirement issues were all cited by fewer than 15% of the physicians as significant issues. When these same physicians were asked whether specific circumstances would bring them back into the practice of obstetrics, 38% responded "yes," 53% responded "no," and 9% did not respond. Of the 29 physicians responding "yes" to this question, 21 indicated that lower malpractice premiums would be necessary to bring them back into the practice of obstetrics. Of these same physicians, 20 indicated that an adequate-sized call group would also be necessary and 18 stated that increased reimbursement would be a necessary factor to get them to return to the practice of obstetrics. Nine physicians indicated that fewer administrative details in the practice of obstetrics would be required, and nine responded that access to care in the community would need to be an issue before they would resume this practice. Of the 29 physicians, only 5 stated that they thought the availability of retraining programs would be necessary to enable them to resume practicing obstetric care.

Of the 67 physicians still practicing obstetrics, 53 responded to the question regarding income generated from their obstetric practice, as well as questions regarding their malpractice insurance premium costs. Physicians in this study generated an average of $53,453 (±$45,190) in the previous year from their obstetric practice. The mean annual total malpractice premium was $15,188 (±$9,971). Several physicians in the study practiced without malpractice insurance coverage. Because many California malpractice insurance programs have incremental rates in the first several years of practice, several of the physicians' policies had not

TABLE 2.—*Reasons Why Family Physicians Include Deliveries in Their Practices*

Category	*Examples of Responses*	*Respondents, %*
Personal satisfaction	"I enjoy doing OB" "I love it"	70
Community service	"OB in rural practice meets community needs" "Increases the quality of care" "Decreases community morbidity"	33
Practice enhancement	"It keeps the practice young" "It brings pediatrics" "It brings whole families into the practice"	25
Integral to the specialty	"Good OB is practiced by family physicians" "It's an opportunity if not an obligation to preserve this in the specialty"	25
Income	"OB is an important part of income" "Income benefits"	16

OB = obstetrics

yet reached the mature rate. When the responses of physicians who had practiced for more than four years were analyzed separately, their mean malpractice insurance premium was $17,282.

An additional analysis was done subtracting the individual insurance premium amount from the amount generated only from the obstetric practice for those physicians who provided both estimates. The mean difference was $30,178. Only five of the physicians who responded to questions on income and malpractice premiums identified income from obstetrics as less than their total malpractice premium. Our analysis shows that all respondents are paying at least the portion of malpractice premium for obstetrics through obstetric services. More than 90% (48/53) of physicians who continued obstetric services are more than paying for their total liability premium from their obstetric practices alone.

Discussion

This study suggests that family physicians continuing obstetrics do so largely because they enjoy it and feel a responsibility to their community. The minority of family physicians practicing obstetrics indicated they do so for financial reasons, although the vast majority more than covered the cost of the total malpractice premium, including the nonobstetric portion. In apparent contrast, family physicians who discontinued obstetrics most frequently cited malpractice premium costs as a reason. This is confusing because these physicians practice in the same area of the state and are insured by the same malpractice insurance carriers. Physicians who continued obstetrics also cared for a higher percentage of Medicaid patients in their practice, which would be expected to be economically disadvantageous. Although the mean age and years in practice differed statistically between the groups, the magnitude of these differences was not striking. A difference that probably is important, however, relates to the size of the communities where these physicians practice. The fact that those who have continued obstetrics are more likely to practice in smaller communities possibly indicates that there is more of a need for them to do obstetrics in their community, making the decision to discontinue obstetrics more difficult.

Whether the enjoyment in delivering babies for those continuing obstetrics was greater than for those who recently discontinued this practice is difficult to assess. There is indirect evidence, however, that those who discontinued it feel that they would not enjoy practicing obstetrics at the present time: the majority indicated they would not resume obstetrics even if substantial changes occurred in the practice environment.

Although this study suggests that it is of economic benefit to practice obstetrics for the majority of those who have continued the practice, what is not known from these results is the amount of time these physicians were required to work to generate the income reported. Although previous studies have shown that physicians who include obstetrics in their practices do not work significantly more hours than those who have never included obstetrics, clearly there is a lifestyle difference.[18] Also, the stress of being in smaller call groups cannot be measured, nor can the anxiety associated with the decreased backup of obstetric specialists that some family physicians experience, particularly in rural areas. Finally, the psychological and emotional costs that physicians go through when they are sued, particularly for obstetric cases, cannot be measured. These issues, as well as factors that have resulted in family physicians continuing to practice obstetrics, need to be addressed by further study.

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Conferences and Reviews

Endoscopic Laser Therapy in Gastroenterology

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Endoscopic laser therapy has become an important and widely used tool in gastroenterology. It has become important for outpatient palliative therapy for ablating obstructing gastrointestinal neoplasms. This method has often circumvented the need for major palliative surgical resections. Caution must be applied to laser therapy for potentially curable malignant neoplasms because, with vaporization of the target tissue, no tissue specimen is available to assure that local or invasive residual carcinoma is excluded. Therefore, in good surgical candidates, surgical resection of potentially curable cancers is always recommended. In the future, however, the combination of refined endoscopic ultrasonography and laser fluorescence techniques may lead to earlier detection, more precise localization, and even curative ablation of gastrointestinal malignancy.

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Over the past ten years, the use of endoscopic laser in clinical gastroenterology has flourished.* In 1981 there were 12 laser units in the United States. Now more than 300 medical centers provide endoscopic laser therapy.[1] It is therefore timely to review the clinical developments in this field. Although laser therapy is used in many different areas of medicine and surgery, we will discuss its use only in gastroenterology.

Historical Considerations

Einstein's theory of relativity laid the theoretic groundwork for Maiman's development of laser technology in 1960.[2] As early as 1963, several investigators had already explored the possibility of using the laser to treat gastrointestinal neoplasia.[3-6] The application of laser to clinical gastroenterology was not practical, however, until Nath and co-workers developed a thin, flexible quartz wave guide or probe in 1973. This probe can conduct the laser beam through the biopsy channel of a conventional endoscope, providing multiple diagnostic and therapeutic uses.[7] Soon thereafter, Frühmorgen, Dwyer and associates published their results with argon laser-induced hemostasis of hemorrhagic gastritis and gastric ulcers in humans.[8,9] Endoscopic laser therapy has since been successfully applied to many gastrointestinal disease processes.

Basic Principles

When an atom is exposed to a sufficient amount of external electromagnetic energy, the electrons of that atom are excited to a higher energy state. With return of the electrons to their initial resting state, energy is released in the form of photons. The released photons then randomly collide with neighboring atoms, resulting in electron excitation that will release additional photons of the same wavelength. This stimulated emission of photons produces laser light. The continuously emitted photons can be directed and amplified by a set of two mirrors producing a laser beam; thus the acronym LASER, from *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation. Unlike sunlight, the beam of light is monochromatic (composed of one wavelength), extremely intense, and easily focused. When absorbed by biologic tissue, the laser energy becomes thermal energy, and, if sufficient temperatures are reached, tissue damage occurs.[10,11]

There are a variety of commercially available lasers. Their names reflect the mediums used to emit photons. The Nd-YAG—neodymium-yttrium-aluminum-garnet—laser, the dye laser, and the argon or carbon dioxide laser use solid, liquid, and gas mediums, respectively. Each laser medium produces a laser beam with a unique wavelength resulting in different absorption properties and tissue effects.[10,11] For example, the argon laser's wavelength is well absorbed by hemoglobin, usually resulting in a 1- to 2-mm depth of tissue penetration. It is therefore useful for photocoagulating superficial blood vessels. The Nd-YAG laser, in contrast, is poorly absorbed by hemoglobin and water but well absorbed by tissue protein, thus making it a better choice for both photocoagulation of deeper vessels and tumor ablation (Tables 1 and 2).[12,13]

TABLE 1.—*Commonly Used Commercially Available Lasers*

Type of Laser	*Usual Wavelength, microns*	*Depth of Tissue Penetration, mm*	*Able to Use in Flexible Endoscope*	*Visible to Human Eye*
Argon	0.51	1-2	Yes	Yes
CO_2	10.60	1	No*	No
Dye	0.54	0†	Yes	Yes
Nd-YAG	1.06	<4	Yes	No

Nd-YAG = neodymium-yttrium aluminum garnet

*A flexible probe that can be used in an endoscope is now available in Japan but not yet in the United States.

†The dye laser has a photoacoustic effect rather than thermally destroying tissue.

Endoscopic Laser Techniques

Most currently used laser endoprobes require a noncontact technique in which the probe tip and the lesion are sepa-

*See also "You Light Up My Life . . . and Liver—Gastroenterologic Laser Therapy in the 1990s" by R. A. Kozarek, MD, on pages 83-84 of this issue.

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rated by approximately 1 cm and the probe tip is aimed as directly or *en face* as possible for maximum effect. The noncontact approach prevents tissue contact with the probe tip that could result in tip heating and damage to the probe. A continuous flow of gas is also delivered coaxially through the probe tip to further prevent tissue adherence and to cool the probe tip. Newer commercially available laser probes, such as the contact endoprobe with a sapphire tip, have been designed for a direct contact approach.[14] This technique can be used with more tangentially located lesions that are not as readily accessible to the en face endoscopic approach of the noncontact laser technique.

TABLE 2.—*Relationship Between Temperature and Tissue Effects in Laser Therapy**

Critical Temperature, °C	*Histologic Event*	*Endoscopic Appearance*
45	Cell death, edema, endothelial damage, vasodilation	Erythema, edema cuff
60	Protein coagulates	Tissue turns white, blood turns black
80	Denatured collagen contracts, blood vessels constrict	Tissue puckers
100	Tissue water boils	Vaporization causes a divot
210+	Dehydrated tissue burns	Blackened tissue disappears or glowing embers appear

*Adapted from Waye et al.[13]

TABLE 3.—*Clinical Applications of Endoscopic Laser Therapy in Gastroenterology*

Application	*Procedure Setting*	*Usual Laser Type*
Tumor ablation		
Esophageal cancer	Outpatient	Nd-YAG
Gastric cancer	Outpatient	Nd-YAG
Colorectal cancer	Outpatient	Nd-YAG
Photodynamic therapy	Inpatient	Argon dye laser
Hemostasis		
Bleeding ulcers	Inpatient	Nd-YAG or argon
Angiomas	Outpatient	Nd-YAG or argon
Radiation proctitis	Outpatient	Nd-YAG or argon
Biliary diseases		
Bile duct stones	Inpatient	Dye laser
Miscellaneous		
Pseudocyst drainage	Inpatient	Nd-YAG
Stricture	Outpatient	Nd-YAG

Nd-YAG = neodymium-yttrium aluminum garnet

Clinical Applications

Endoscopic laser therapy has many therapeutic applications. The clinical problem and desired effects determine the type of laser used. Most treatments are safely done on an outpatient basis without much more discomfort than with routine endoscopies (Table 3).

Tumor Ablation

Endoscopic laser treatment is useful for the palliative treatment of incurable gastrointestinal malignancy and in those patients who are poor surgical candidates. Laser therapy has also been successfully used to remove large benign gastrointestinal neoplasms with high malignant potential.[15,16] Its use, however, as a primary curative therapy for early localized malignant neoplasms is still under investigation.[17,18]

Esophageal carcinoma. In the United States, patients who present with esophageal cancer are generally incurable with all conventional therapies. Therapeutic goals are the relief of obstruction and bleeding. Since Fleischer and Kessler first used the laser endoscopically to treat esophageal carcinoma in 1982, laser ablation has become a major tool for tumor palliation.[19]

Laser therapy can usually be done on an outpatient basis. Preparation is the same as for an upper endoscopy. As with other endoscopic procedures, patient comfort is maintained with intravenous sedation and topical pharyngeal anesthesia.

Laser treatment is preferentially performed in the distal to proximal direction to maximize visualization and minimize the risk of perforation. Thus, a strictured esophageal lumen must be wide enough to accept the endoscope. If luminal stenosis does not allow free passage of the endoscope, mechanical dilation of the narrowed area is required before successful laser treatment. The laser probe is then inserted through the biopsy channel of the endoscope and aimed at the malignant tissue under direct visualization. The laser coagulates and vaporizes the obstructing tissue, creating a wider lumen (Figure 1).

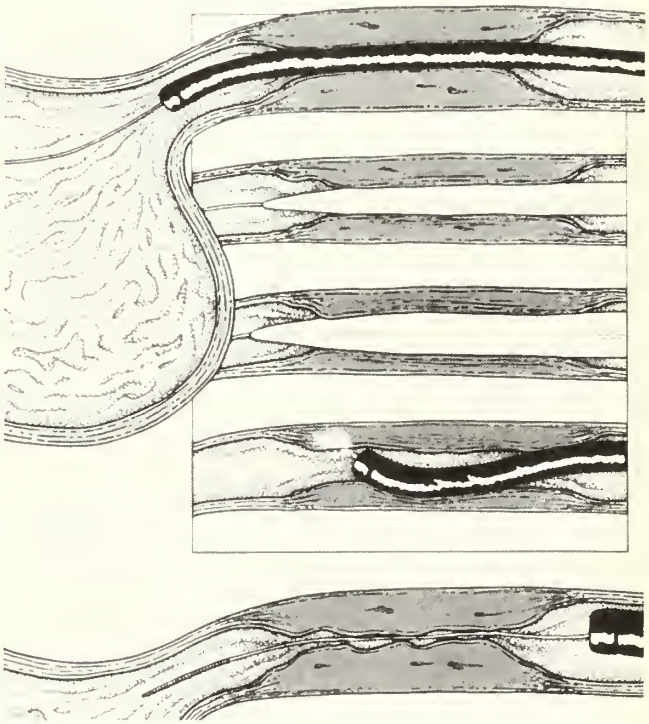

Figure 1.—The tumor shown is partially occluding the esophageal lumen. Although the endoscope can pass through the strictured area, it cannot be maneuvered effectively to allow for laser treatment of the tumor mass. With mechanical dilation (inset), the endoscope with laser probe can now be used to fulgurate the tumor in a distal to proximal direction (from Waye et al[13]).

Contact endoprobes, noncontact endoprobes, and even nude fibers (laser fibers whose distal ends are progressively destroyed as they are used) have been used successfully to ablate esophageal tumors. Contact coagulation can be useful in a very stenotic or completely occluded lumen in which target tissues cannot be approached en face with the endoscope.[20(p143)] A small prospective study comparing the efficacy

of contact with noncontact Nd-YAG laser therapy found no difference between the two methods in the number of treatment sessions required, the relief of dysphagia, or the occurrence of complications. The esophageal lumens of both groups were relatively patent, however, so an advantage may not have been elicited.[14] Further study of the potential benefits of the contact endoprobe technique is needed.

The number of sessions required to provide adequate palliation depends on the severity of the stenosis. Although there are proponents of only a single session of treatment, generally two or three sessions, each session scheduled every two to three days, are required.[21]

More than 90% of patients who are treated with laser therapy have a marked abatement of dysphagia. Although the result is best in those patients with tumors that are less than 5 cm long and located in straight segments of the mid and distal esophagus,[22] technical success in achieving luminal patency does not always correlate directly with the patient's overall clinical state. Because of refractory dysphagia, odynophagia, and anorexia, 10% of these patients will be unable to maintain their weight.[22-24] Furthermore, the effects of laser therapy may be short-lived, and follow-up sessions may be required. These sessions may consist of additional laser treatments, mechanical dilation, or both.[24] If the tumor recurs in a more submucosal than exophytic pattern, additional laser therapy is increasingly less effective.[25]

Exophytic carcinomas of the mid and distal esophagus are ideally suited to laser ablation. Laser therapy for carcinomas of the cervical esophagus and submucosally located tumors is less effective and has a higher complication rate. In fact, some think that laser treatment of these latter tumors is relatively contraindicated. Absolute contraindications to laser treatment are similar to those of upper endoscopy. These contraindications are the inability to cooperate, a known or suspected perforated viscus, and unstable cardiac or pulmonary conditions.[22,26]

The major complication of endoscopic laser therapy is perforation, with an overall incidence of 5% to 8%. Previous radiation therapy and a proximal location of tumor may increase the risk of perforation. Minor side effects such as abdominal distension caused by air insufflation during treatments and transient chest pain occur 10% of the time. Substantial bleeding, sepsis, and systemic side effects are rare.[27-29] Laser therapy has an overall mortality rate of less than 1%.[22-24,26]

Other accepted palliative treatments of esophageal cancer include the endoscopic placement of endoprostheses, surgical resection, and radiation and chemotherapy. Comparisons of laser treatment with intraesophageal prostheses suggest that both methods are equally effective in lessening dysphagia in the straight segments of the esophagus. The prosthesis is slightly better at resolving dysphagia when the tumor is located at the gastroesophageal junction.[30] Endoprosthesis placement across the gastroesophageal junction, however, is associated with significant reflux complications.[31] Because endoscopic treatment of the upper esophagus is technically difficult, neither laser treatment nor prostheses are particularly effective at providing symptom relief for obstructive tumors in the cervical esophagus.

Although prostheses have greater procedure-related morbidity than laser treatment, there is no significant difference in procedure-related mortality and overall survival. Complications of endoprosthesis placement include tube migration, blockage, pressure necrosis, erosion into adjacent structures, and death.[24-26,31,32]

Both laser treatment and surgical resection of incurable esophageal carcinoma result in equally favorable symptomatic relief. Surgical treatment is associated with a substantially higher perioperative death rate, ranging from 10% to 30%.[27] Endoscopic laser therapy has a less than 1% mortality and offers the additional advantage of an outpatient setting.[31] Despite successful laser treatment requiring multiple endoscopic sessions, its overall cost is still much less than the cost of a palliative operation.[26]

There are no studies that compare the efficacy of laser therapy with that of radiation and chemotherapy. Laser therapy, however, may have more immediate results, may require fewer treatment sessions and hospital visits, and is probably less expensive. The morbidity and mortality of radiation therapy and laser therapy are probably comparable.[26] There are no effective chemotherapeutic regimens for adenocarcinoma of the esophagus, but several drug regimens have produced partial and complete responses in patients with squamous cell esophageal cancer.[33(p859)]

In conclusion, laser therapy for the relief of malignant esophageal obstruction is as effective as surgical therapy and endoprosthesis placement. Laser therapy has low procedure-associated morbidity and mortality compared with these other methods. There is no evidence that any therapy prolongs survival.

Gastric carcinoma. Endoscopic laser therapy is used primarily as a palliative treatment to relieve obstruction and to prevent recurrent bleeding in patients with gastric cancer. Most gastric carcinomas that are amenable to laser therapy are located near the gastroesophageal junction and present with obstructive symptoms. One to three sessions of endoscopic laser therapy may lead to notable symptomatic improvement.[28]

Contraindications to and complications of laser therapy for gastric cancer are similar to those previously described for esophageal cancer. Although direct comparisons are not available, laser therapy is probably less expensive and has less morbidity than palliative surgery.[28,34]

Japanese investigators are studying the use of endoscopic laser therapy for the curative treatment of localized mucosal gastric carcinoma. They have reported 74% to 85% five-year survival in a highly selected group of patients treated with the laser alone.[17,18,35] These results are similar to those of conventional surgical therapy, although comparative trials are lacking.

Colorectal carcinoma. Laser therapy for colorectal cancer provides relief of obstruction and bleeding in patients who are poor surgical candidates.[36-38] Although treatment is traditionally reserved for patients with rectal cancer because of easy endoscopic access and its purported safety, the treatment of more proximal lesions is now being reported.[39,40]

About two to five outpatient sessions are required to create a lumen large enough to allow the passage of feces and gas. To maintain luminal patency, follow-up sessions are usually required every four to eight weeks. Despite successful laser treatment requiring multiple endoscopic sessions, the overall cost is considerably less than that of surgical palliation.[41]

Complications of rectal laser therapy include perirectal abscess formation, anal stenosis, with incidences of 2% to 3% and 2% to 5%, respectively, and perforation. Rectal per-

foration is usually contained in the perirectal space and can often be managed with intravenous antibiotic therapy and bowel rest. Perforations in the more proximal colon (above the peritoneal reflection) result in soilage of the free peritoneal space and often require surgical intervention. Overall reported colorectal perforation rates range from 3% to 10%. The mortality of colorectal laser therapy is less than 1%.[39,42]

In addition to palliative treatment of colorectal cancer, the Nd-YAG laser has been used to vaporize large, sessile, benign polyps, which have a high malignant potential and are technically difficult to remove with endoscopic polypectomy techniques. A recent study showed a negligible incidence of malignant occurrence and no difference in life expectancy with laser treatment of these lesions as compared with surgical resection.[15] An equally large study, however, demonstrated a significant incidence of malignant occurrence in those patients who underwent endoscopic laser treatment alone.[36] Currently, polyps not amenable to endoscopic polypectomy should be surgically resected in all suitable surgical candidates.

In summary, laser therapy is particularly useful in recanalizing obstructive malignant rectal and colonic lesions and in removing large sessile polyps in poor surgical candidates. Patients with a reasonable surgical risk, however, should have their carcinomas or large polyps removed surgically. Possible advances in endoscopic ultrasonography may eventually determine if residual neoplastic tissue is present after laser treatment, thus providing a potentially curative role for laser therapy alone.

Photodynamic therapy. Although still experimental and in its infancy, laser photodynamic therapy has been used to treat thousands of patients with various types of cancer.[43] The basic principles and techniques of photodynamic therapy are simple. An exogenous photosensitizer, which is administered intravenously, is selectively retained by malignant target tissues. A laser with a specific wavelength is then applied to the sensitized tumor tissue by a diffuser fiber that distributes the beam over a wide surface area.[44] With exposure to the laser light, intracellular photochemical reactions are initiated, resulting in fluorescence of and damage to (including cell lysis) the sensitized tissues. The theoretic result of this therapy is the selective destruction of malignant tissue with sparing of the surrounding normal tissue. Current clinical protocols use hematoporphyrin derivatives as photosensitizing agents and the argon dye laser as the source of the laser light.[43]

Although photodynamic therapy is an increasingly popular technique for skin, bronchial, and bladder carcinomas, its use in gastrointestinal malignancy has been limited. The Japanese with their aggressive esophagogastric carcinoma screening program have applied these techniques to the treatment of superficial localized tumors. Some endoscopists are using a contact probe that buries the laser fiber in the mucosa to increase treatment effectiveness.[17] Their success rates in these small case series vary, with cure rates of 0% to 80%.[45,46]

Photodynamic therapy has also been used as a palliative treatment of patients with obstructing esophagogastric and colonic tumors. The obstruction can be relieved in 50% to 100% of cases, but no direct comparisons with standard laser ablation therapy are currently available.[29,47,48]

The most common complication of photodynamic therapy with hematoporphyrin derivatives is skin photosensitivity that resembles the skin manifestations of porphyria. Patients may need to avoid excessive sun exposure for as long as 12 weeks after therapy.[47] Severe cutaneous sunburns are reported in 3 of 54 patients (6%) in one study.[49] Serious complications including mediastinitis, stricture formation, bronchoesophageal fistula, and perforation may occur in as many as 22% of patients treated.[49,50] These complications are more frequently encountered when photodynamic therapy is applied to obstructing lesions.[45,46,49,50]

The currently used technique of photodynamic therapy has several limitations. The available hematoporphyrin derivatives are not as selectively retained in tumor tissue as once thought. Nor is the ideal dosing of these photosensitizing agents known. Furthermore, their specific light absorption spectrums mandate the use of lasers that can produce only superficial tissue ablation.

In summary, photodynamic therapy for gastrointestinal tumors is currently an experimental tool and cannot be recommended as a routine palliative or curative therapy. With the refinement of laser delivery systems and the type and dosing of photosensitizing agents, photodynamic therapy may soon play an active role in treating early and advanced gastrointestinal malignancy.

Hemostasis

To establish the efficacy of a specific therapy for gastrointestinal bleeding, it is important to know the natural history and prognosis of the lesions that are to be treated. For example, in 80% of cases, upper gastrointestinal bleeding stops spontaneously; hence, establishing the efficacy of a specific therapy is difficult, often requiring a large number of patients from multicenter trials to minimize type II errors. It is also particularly important to identify the subgroup of high-risk patients who are likely to continue to bleed and who have increased morbidity and mortality if early therapeutic intervention is not provided.[51] With these epidemiologic considerations in mind, we address the efficacy of lasers in the management of gastrointestinal bleeding.

Endoscopic laser therapy was the first and most extensively studied thermal hemostatic procedure. Initial emphasis was placed on the argon laser because it is absorbed primarily by hemoglobin and has a shallow 1- to 2-mm depth of effect. The argon laser, therefore, seemed perfectly suited for coagulating a superficial blood vessel without perforating the thin underlying viscera. The Nd-YAG laser, on the other hand, because of its greater depth of penetration was feared to have an unacceptably high perforation rate.[51] Data from subsequent clinical studies suggested similar safety and efficacy, however.[52-54] The argon laser is more difficult to use in a bloody field because its energy is often absorbed by overlying blood clots and not the deeper target vessels. The Nd-YAG laser is now generally preferred by most endoscopists.[1]

Peptic ulcer disease. Patients admitted to hospital with bleeding peptic ulcers generally have a fairly benign course with almost no mortality. Patients who rebleed during their initial hospital stay, however, may have a mortality as high as 22%.[51] This grim prognosis has led to intensive attempts to differentiate prospectively those patients who are more likely to rebleed. Several endoscopic criteria that convey an increasing risk of rebleeding have now been identified. The main criteria established at the time of the initial endoscopy are the presence of an ulcer with active bleeding and the presence of a nonbleeding visible blood vessel in the ulcer base. If actively bleeding, as many as 85% of patients may

rebleed during the initial hospital stay. If visible nonbleeding vessels are present, there is a 50% or greater incidence of rebleeding.[55]

Prospective randomized studies of laser therapy for upper gastrointestinal tract bleeding have generated conflicting data,[52-54,56-59] but if these data are analyzed by patient subgroups according to their potential rebleeding risk, the efficacy of laser therapy can generally be demonstrated in the high-risk group. In addition to successful initial hemostasis with laser therapy in these patients, most studies show a significant reduction in the incidence of rebleeding, the number of units of blood required, and the need for emergent surgical intervention.[52-54,56-58] In contrast, no favorable effects of laser therapy can be shown in patients without visible vessels or active bleeding, presumably because their risk of rebleeding and death from bleeding is so low.[52-59]

The role of laser therapy for bleeding ulcers is now less clear with the introduction of two portable bedside endoscopic techniques: injection therapy and electrothermal coagulation. Endoscopic injection therapy is an increasingly popular, technically easy procedure. Epinephrine or hypertonic saline or ethanol solution is administered into the bleeding target vessel and surrounding tissues under direct endoscopic vision. The required accessories for this technique are few, mobile, and inexpensive. Electrothermal coagulation therapy uses contact thermal probes such as the multipolar and heater probes to simultaneously tamponade a bleeding vessel and deliver thermal coaptive energy.[55] Although direct comparisons of laser therapy with these devices are few, injection therapy and thermal probe approaches appear as, if not slightly more, effective than the laser.[55,60,61] Injection therapy offers the additional advantage of few technical failures, whereas the laser and thermal probes cannot be used in about 10% of lesions because of an inability to approach the target lesion with the probe.[1,56,59]

Complications of laser therapy for bleeding ulcers include a 0% to 2% perforation rate in controlled studies with experienced endoscopists.[51,59] Laser-induced massive bleeding has been reported but is only a rare complication of this procedure.[51]

In conclusion, endoscopic laser therapy effectively provides acute hemostasis for patients with actively bleeding ulcers and decreases the number of units of blood required and the need for emergent surgical repair. The more portable, less expensive, and less technically demanding nonlaser electrical thermal probes and, more recently, injection therapy have, however, essentially replaced the laser in the current management of patients with bleeding ulcers.

Gastrointestinal vascular malformations. Gastrointestinal vascular malformations—that is, angiomas, arteriovenous malformations, angiodysplasias, vascular ectasias, and "watermelon" stomach—are a diverse group of lesions with poorly defined natural histories. They make up a small but substantial percentage of all causes of gastrointestinal bleeding.[62] Several uncontrolled studies have generally reported efficacy of both argon and Nd-YAG lasers in decreasing short-term transfusion requirements and the incidence of recurrent bleeding in these disorders.[63-71] Until, however, the natural history of vascular malformations is better defined with well-designed controlled prospective studies comparing endoscopic laser therapy with other treatment modalities, including medical therapy and surgery,[72] laser therapy's short- and especially its long-term efficacy should be accepted with caution.

Chronic radiation proctitis. Recurrent lower intestinal bleeding due to chronic radiation injury occurs in 2% to 11% of patients who have received abdominopelvic radiation therapy.[73] More than 90% of all gastrointestinal radiation injuries involve the rectum and rectosigmoid colon.[73] Patients with chronic radiation proctitis present with tenesmus, crampy abdominal pain, and bloody diarrhea, usually 6 to 24 months after receiving radiotherapy.[73,74] Those patients in whom anemia develops from severe recurrent bleeding rarely respond to traditional medical therapy. Traditional therapy has included the empiric use of steroid enemas and sulfasalazine. Although the use of these anti-inflammatory agents is appropriate for inflammatory mucosal lesions such as ulcerative proctitis, the characteristic lesion of chronic radiation proctitis has essentially no active inflammation and often fails to respond to these medications. In fact, chronic radiation "proctitis" is a misnomer. The mucosa is actually often atrophic and fibrotic and contains many fragile bleeding neovascular lesions.[74] Patients for whom medical therapy fails are often treated with diverting colostomy or proctosigmoid resection. Unfortunately, these surgical procedures may fail to prevent recurrent bleeding and are associated with high morbidity and mortality.[75-77]

The use of the argon and Nd-YAG lasers for the treatment of severe chronic radiation proctitis has been reported in several case series. These series showed a decrease in both transfusion requirements and the incidence of rebleeding, with only minor complications.[73,78-81] Laser therapy appears promising for the treatment of chronic refractory radiation proctitis. These early positive results await confirmation with further clinical experience.

Biliary Disease

About 90% of common bile duct stones can be successfully removed endoscopically. The remaining 10% of stones are often technically too difficult to extract endoscopically because of their large size.[82] In the past few years, several techniques including extracorporeal shock wave lithotripsy, solvent dissolution, and electrohydraulic lithotripsy have been developed to fragment these large stones, facilitating their endoscopic removal.[83,84]

A recent entry into this field is the flash-lamp dye laser.[85,86] Its laser beam can be transmitted by a quartz fiber that is placed through the duodenoscope in direct contact with the common bile duct stone. Because of the differences between the light absorption properties of stones and tissue, fragmentation of stones can usually be achieved without simultaneously damaging the surrounding duct. This method should theoretically be effective for all types of common bile duct stones, including those that are calcified. This technique has also been applied successfully to gallbladder stones and intrahepatic stones through a percutaneous tract. Experience with endoscopic and percutaneous laser lithotripsy is, however, still limited. Its efficacy compared with that of other existing procedures and its potential complications will require further study.[82,85-88]

A few case reports describe the endoscopic laser treatment of malignant and benign biliary tract strictures and tumors of the ampulla of Vater. A few endoscopic sphincterotomies have also been done with the laser. The patients,

however, were generally either poor surgical candidates or more conventional endoscopic and surgical treatments had failed.[89-94]

Miscellaneous Disorders

Multiple reports from small case series have described interesting but not generally accepted laser applications. These include the treatment of duodenal and esophageal webs and short benign gastrointestinal strictures.[95] The drainage of pancreatic pseudocysts through a laser-induced fistulous tract from the gastric or duodenal wall to the underlying adherent pseudocyst has also been reported.[96-99]

New Directions

Attempts are now under way to develop less expensive, smaller, and more portable laser units. If successful, lasers will become more suitable for emergency bedside use.

With the introduction of high-resolution endoscopic ultrasonography, the ability to detect small curable malignant lesions noninvasively may be within reach. The combination of this technique with photodynamic therapy is currently under investigation and has the potential to both detect and treat these tumors.

Other exciting developments are new laser probe delivery systems. Sapphire-tipped and ceramic endoprobes that use a contact approach are now available and may facilitate both tumor debulking and hemostasis.[14,100] New lateral-aiming probes are now being developed.[101] These probes will be ideal for eccentrically located lesions that cannot be approached in the traditional en face manner. Another possible advance is the use of the laser balloon that when inflated conforms to a stricture and allows for a circumferential dispersion of laser energy and the destruction of tissue.[102]

Low-volume water infusion rather than high-flow gas has been used successfully to maintain a clean field during noncontact laser application.[66] The benefits of this new approach are not only the ability to clean a bloody field more effectively but also the avoidance of gaseous overdistension during the procedure.

A flexible probe for the carbon dioxide laser is now available for endoscopic use in Japan. The carbon dioxide laser's local superficial cutting and coagulating effects, which simulate those of a surgical scalpel, may be used for small superficial lesions such as arteriovenous malformations of the cecum with less fear of perforation. Other lasers that simulate a surgical scalpel are also now available. Examples of these include the erbium-YAG and the holmium-YAG lasers. The limiting factor in the erbium-YAG laser's development has been and remains the inability to design a durable fiber for endoscopic use.[66,95]

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Do We Need an Intravenous Fluoroquinolone?

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Intravenous ciprofloxacin, the first parenteral fluoroquinolone available in this country, represents another class of antimicrobial agents from which physicians must choose when treating nosocomial infections. Fluoroquinolones are bactericidal antimicrobial agents that act by inhibiting DNA gyrase. They are active in vitro against most gram-negative bacteria and methicillin-susceptible staphylococci. Activity against anaerobic bacteria and streptococci is poor. The rapid development of bacterial resistance in centers with high quinolone usage is of great concern. Resistance develops most commonly in *Pseudomonas aeruginosa* and staphylococci. Resistance emerges most often when quinolones are used to treat chronic infections or in patients with poorly drained abscesses, necrotic tissue, or indwelling catheters. Clinical trials have shown ciprofloxacin to be as effective as ceftazidime in the treatment of infections caused by gram-negative bacteria. Although the overall frequency of side effects to fluoroquinolones is low, seizures and allergic reactions have been attributed to their use. Ciprofloxacin inhibits the metabolism of theophylline, and morbidity and death have been reported in patients taking the two drugs concomitantly. Parenteral fluoroquinolones should be reserved for the treatment of gram-negative bacterial infections in patients in whom standard agents cannot be used.

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Fluoroquinolone antimicrobial agents are structurally related to nalidixic acid. The fluoroquinolones were developed to avoid the problem of a rapid emergence of resistant gram-negative bacteria that is seen during nalidixic acid therapy. Oral norfloxacin became available in the United States in 1986 and was followed by oral ciprofloxacin in 1987. Recently ofloxacin became the third oral fluoroquinolone available for use in this country. The oral fluoroquinolones have been used widely for various bacterial infections, especially infections of the urinary tract, bone, and skin and soft tissue. In early 1991, the US Food and Drug Administration (FDA) approved an intravenous form of ciprofloxacin. Intravenous ciprofloxacin is indicated for the treatment of mild to moderate lower respiratory tract infections, skin and skin structure infections, and bone and joint infections caused by susceptible pathogens. The drug also is approved for the treatment of mild, moderate, and severe and complicated urinary tract infections caused by susceptible pathogens ("CIPRO® IV Package Insert," Miles, Inc, West Haven, Conn, 1991). An intravenous form of ofloxacin may be available soon. In this article we review the published literature on intravenous ciprofloxacin as a representative fluoroquinolone and address the question of whether this agent is a necessary addition to the therapeutic armamentarium against infectious diseases.

Mechanism of Action

Ciprofloxacin is an inhibitor of DNA gyrase (topoisomerase II), an enzyme that introduces negative supercoils in DNA.[1] DNA gyrase is composed of two A subunits, encoded by the *GYRA* gene, and two B subunits encoded by the *GYRB* gene. The A subunits mediate the breakage and rejoining of DNA, while the B subunits are responsible for energy transduction and adenosine triphosphate hydrolysis during gyrase activity.[2] Quinolones inhibit the resealing of DNA double strands by the A subunits, leading to interference with DNA replication, a segregation of bacterial chromosomes, transcription, and other cellular processes.[3,4] The inhibition of DNA gyrase alone does not account for ciprofloxacin's bactericidal activity; other mechanisms have not yet been determined.[2]

Ciprofloxacin crosses the outer membrane of gram-negative organisms by a passive diffusion through porin channels.[5] The mechanism by which quinolones penetrate the inner membrane of gram-negative bacteria is unknown. Some bacteria may possess an energy-dependent efflux mechanism.[5]

In Vitro Activity

Ciprofloxacin is effective against a broad gram-negative spectrum including *Pseudomonas aeruginosa*, Enterobacteriaceae, *Haemophilus* species, and *Neisseria* species.[6] The drug is active against many staphylococcal organisms, although resistance is an increasing problem. In general, activity against streptococci and anaerobic organisms is poor. Ciprofloxacin also has limited in vitro activity against *Mycobacterium* species, *Chlamydia* species, *Mycoplasma* species, rickettsia, and *Plasmodium falciparum*.[4,7] With the exception of some mycobacterial infections, clinical trials do not support the use of ciprofloxacin in the treatment of infections caused by these organisms. Table 1 lists the minimum inhibitory concentration for 90% of bacterial strains.[3,4,6,8-11] Ciprofloxacin exerts a substantial post-antibiotic therapy effect against *Staphylococcus aureus* and most gram-negative bacteria.[12] When ciprofloxacin is combined with β-lactam antibiotics or aminoglycosides, the combinations are rarely synergistic or antagonistic.[13] When combined with antipseudomonal penicillins, however, synergy occurs against 20% to 50% of *P aeruginosa* organisms. Although rifampin and ciprofloxacin may be antagonistic against staphylococci,

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the combination has been used successfully to treat a highly selected population of intravenous drug users with right-sided *S aureus* endocarditis.[14] Problems with bacterial resistance to ciprofloxacin are discussed in the next section.

Resistance

When oral ciprofloxacin was first released for general use in the United States in 1987, it was thought that resistance to the drug would be uncommon.[15] Although resistance rates have been low for most organisms, *P aeruginosa* and staphylococcal resistance has been increasing at an alarming rate. There are two major mechanisms of resistance to quinolones.[16] The most common is an alteration in bacterial DNA gyrase leading to decreased quinolone binding.[16] The other mechanism of resistance is decreased drug accumulation in the bacterial cell. This mechanism may involve an active efflux of ciprofloxacin by bacteria.[16] Bacteria with high-level resistance to ciprofloxacin usually possess both resistance mechanisms. Plasmid-mediated quinolone resistance has not been detected to date.[17]

TABLE 1.—*Ciprofloxocin In Vitro Susceptibility Dota*

Organism	MIC_{90}, μg/ml*†
Acinetobocter spp	0.25-1.0
Citrobocter spp.	0.03-0.39
Enterobocter spp	0.03-0.5
Escherichio coli	0.03-0.25
Hoemophilus influenzoe	0.01-0.06
Klebsiello oxytoco	0.03-0.25
Klebsiello pneumonioe	0.05-1.0
Morgonello morgonii	0.01-0.12
Neisserio gonorrhoeoe	0.01-0.06
Proteus mirobilis	0.03-0.25
Proteus vulgoris	0.03-0.25
Providencio stuortii	0.25-2.0
Pseudomonos oeruginoso	0.12-2.0
Serrotio morcescens	0.06-2.0
Enterococcus spp	2.0-4.0
Stophylococcus aureus	0.5-1.0
Stophylococcus oureus, methicillin-susceptible	0.5-1.0
Stophylococcus oureus, methicillin-resistant	2.0-64
Stophylococcus epidermidis	0.5-1.0
Streptococcus pneumonioe	1.0-2.0

MIC_{90} = minimum inhibitory concentration for 90% of strains, spp = species

*From Campoli-Richards et al,[3] Hooper and Wolfson,[4] Neu,[6] Barry and Fuchs,[8] Fuchs et al,[9] Smith,[10] and Maple et al.[11]

†Bacteria with a minimum inhibitory concentration of ≤ 1 μg/ml are considered susceptible, and bacteria with a minimum inhibitory concentration > 2 μg/ml are considered resistant.

Numerous reports of increasing *S aureus* and coagulase-negative staphylococcal resistance to ciprofloxacin and other quinolones have appeared recently.[18-20] Resistance rates are highest in methicillin-resistant *S aureus* (10% to 83%), and such resistance can develop rapidly in institutions with high ciprofloxacin use.[18,20] Skin cultures were positive for ciprofloxacin-resistant coagulase-negative staphylococci in 78% of neutropenic patients with leukemia who received ciprofloxacin compared with only 17% of patients in a control group.[19] Cross-resistance among quinolones is generally complete.[11] Pneumococcal superinfections have occurred in patients receiving ciprofloxacin.[21] Resistance also has been reported in *Enterococcus faecalis*.[22] Ciprofloxacin should only be used to treat susceptible gram-positive bacterial infections when other agents cannot be used.

The emergence of resistance to ciprofloxacin during therapy has been reported in most gram-negative bacteria including *Escherichia coli*,[23] *Enterobacter cloacae*,[24] *Serratia marcescens*,[25] *Klebsiella* species,[16] *Salmonella*,[26] and *P aeruginosa*.[27] Resistance emerges most often when ciprofloxacin is used to treat chronic infections or when poorly drained abscesses, indwelling catheters, or necrotic tissue are present.[28] A study conducted at the Pittsburgh (Pennsylvania) Veterans Affairs Medical Center showed that the previous receipt of a quinolone was the most important risk factor for the development of quinolone-resistant gram-negative bacteria[29]: 15% of all gram-negative organisms were ciprofloxacin-resistant, 75% of which were associated with clinical infection.[29] Most of the resistant organisms were cultured from urine, sputum, and wound specimens. Strategies for decreasing the emergence of resistance to quinolones include optimal dosing, monitoring for the development of resistance, combination drug therapy, and a restricted use of the drug to those circumstances where its use clearly is appropriate (discussed later).[16]

Pharmacokinetics

Following the intravenous infusion of 400 mg of ciprofloxacin, mean peak serum levels of 4.6 μg per ml are achieved ("CIPRO® IV Package Insert"). This level is similar to peak levels produced by a 750-mg oral dose of ciprofloxacin ("CIPRO® IV Package Insert"). The bioavailability of oral ciprofloxacin is about 80%. A 400-mg dose of intravenous ciprofloxacin is equivalent to a 500-mg oral dose as measured by the area under the serum concentration time curve. Intravenous ciprofloxacin doses of greater than 400 mg cannot be recommended because adequate clinical trials have not been done. The volume of distribution of ciprofloxacin is about 3.5 liters per kg of body weight, and plasma protein binding of the drug is 16% to 40%.[3] Ciprofloxacin is distributed well to most body tissues and fluids including the bronchial mucosa,[30] myocardium and skeletal muscle,[31] kidney,[4] prostate,[32] and skin.[3] Ciprofloxacin cerebrospinal fluid levels are only 10% of the concomitant serum levels, however.[3] Ciprofloxacin is eliminated primarily as unchanged drug in the urine.[3] About 10% to 20% of the drug is converted to four metabolites. The elimination half-life is 3.4 to 6.9 hours[3] but is prolonged to about 10 hours in patients with renal failure.[33] Minimal amounts of ciprofloxacin are removed by peritoneal dialysis or hemodialysis.

Clinical Trials

Intravenous ciprofloxacin for the treatment of many infections has been studied in open and comparative trials. In most of these studies, ciprofloxacin was used in doses of 200 to 300 mg every 12 hours. With the exception of urinary tract infections, however, the FDA has approved only a dosage regimen of 400 mg every 12 hours. Open, noncomparative trials have shown parenteral ciprofloxacin to be effective in the treatment of patients with bacteremia[34] and lower respiratory tract infections caused by gram-negative bacteria.[35,36] Clinical response rates have been about 60% in patients with lower respiratory tract infections and 95% in patients with bacteremia. Other noncomparative trials suggest that ciprofloxacin is effective in patients with a variety of serious infections including urinary tract infections, osteomyelitis, soft-tissue infections, and endocarditis.[37-40] The majority of infections were caused by gram-negative bacteria, but some were

caused by staphylococci and streptococci. Clinical response rates ranged from 76% to 96%. In studies that evaluated the efficacy of ciprofloxacin in the treatment of polymicrobial infections, ciprofloxacin was often combined with an antibiotic with activity against gram-positive or anaerobic bacteria.

Most comparative trials that involve ciprofloxacin have compared the use of the quinolone with ceftazidime in the treatment of infections caused mainly by gram-negative bacilli. The two drugs have been compared in the treatment of lower respiratory tract infections,[41-43] skin and soft-tissue infections,[44,45] urinary tract infections,[41] and a variety of serious gram-negative infections.[46-50] Clinical response rates were not significantly different in most studies and ranged from 75% to 100% in patients treated with ciprofloxacin versus 58% to 97% in patients treated with ceftazidime. A comparative evaluation of published clinical trials is difficult because most studies involved a small number of patients, used different criteria for patient selection, often did not state if patient groups were similar in relevant variables such as underlying medical conditions and severity of illness, and used different definitions of results. Other comparative studies have found ciprofloxacin to be as effective as imipenem and the combination of ticarcillin disodium and clavulanate potassium in the treatment of serious gram-negative infections.[51,52] These trials also included such small numbers of patients that they have low power to detect significant differences, even at levels that might be clinically meaningful. Ciprofloxacin in combination with penicillin, azlocillin, teicoplanin, or netilmicin appears to be as effective as standard therapy in the treatment of infections in febrile neutropenic cancer patients.[53-56] Failure rates (33% to 35%) and superinfection rates are, however, too high when ciprofloxacin is used as monotherapy.[55-57] Most treatment failures and superinfections were caused by gram-positive bacteria.

Clinical trials have not compared the efficacy of oral ciprofloxacin with the parenteral form of the drug. Unless a patient is in shock or taking medication that will interfere with the absorption of oral ciprofloxacin—such as aluminum- or magnesium-containing antacids—it is unlikely that a patient who fails to respond to oral ciprofloxacin will respond to the intravenous form of the drug. Parenteral fluoroquinolones that may become available in the near future will not likely offer notable advantages in clinical efficacy over intravenous ciprofloxacin.[4]

Side Effects

As with other fluoroquinolones, ciprofloxacin is generally well tolerated and safe. The incidence of side effects is about 15%, most of which have been mild or moderate in severity.[58] Ciprofloxacin therapy has to be discontinued because of adverse reactions in 1.5% of patients.[59] The rate of side effects is similar to that seen with the use of most β-lactam antibiotics, but, as previously mentioned, most of the clinical trials that involve intravenous ciprofloxacin studied doses of 200 to 300 mg every 12 hours. It is possible that the incidence of adverse effects, especially neurotoxicity, may be higher when doses of 400 mg every 12 hours are used. Patients who are likely to require parenteral fluoroquinolone therapy may be at an increased risk of side effects because of their poor underlying condition. Local reactions at the infusion site and gastrointestinal side effects occur most frequently and include nausea, vomiting, diarrhea, and abdominal pain.[4] Pseudomembranous colitis also has been reported.[60] Like its parent drug nalidixic acid, ciprofloxacin causes a wide variety of central nervous system reactions including anxiety, nervousness, dizziness, depression, nightmares, hallucinations, psychoses, and seizures ("CIPRO® IV Package Insert").[60-62] The mechanism of ciprofloxacin-induced seizures appears to be an inhibition of the binding of γ-aminobutyric acid, an inhibitory neurotransmitter, to its central nervous system receptors.[63] Patients with epilepsy, head trauma, cerebrovascular disease, renal failure, or alcoholism are predisposed to ciprofloxacin-induced seizures.[60] The use of theophylline and nonsteroidal anti-inflammatory agents may also increase the risk of seizures when administered with quinolones.[58,64] Allergic reactions, including anaphylactoid reactions,[65] serum sickness,[66] and allergic interstitial nephritis,[67] have been attributed to the use of ciprofloxacin. A literature search on the incidence of drug-induced interstitial nephritis reported since 1987 revealed that there are more articles on ciprofloxacin-induced interstitial nephritis than any other single drug. Other reported side effects include photosensitivity,[68] blurred vision, joint pain, and cardiopulmonary arrest ("CIPRO® IV Package Insert"). Ciprofloxacin causes cartilage damage in young animals; therefore, it is recommended that the drug not be administered to children and pregnant women ("CIPRO® IV Package Insert").[60]

Drug Interactions

Intravenous ciprofloxacin has a number of important interactions with other drugs,[69] the most important being the inhibition of theophylline metabolism. Ciprofloxacin reduces theophylline clearance by about 30% and increases serum levels by about 23%.[70] Morbidity and death have been reported in patients taking ciprofloxacin and theophylline concomitantly ("CIPRO® IV Package Insert").[71] If ciprofloxacin must be given to patients taking theophylline, serum levels of theophylline should be monitored closely.[72] Ciprofloxacin also interferes with the metabolism of caffeine.[73] It potentiates the hypoprothrombinemic effects of

TABLE 2.—*Ciprofloxacin Dosage Recommendations**

Site of Infection	*Severity*	*Dosage Regimen, mg*
Urinary tract	Mild/moderate	200 every 12 h
Urinary tract	Severe/complicated	400 every 12 h
Lower respiratory tract, skin and skin structure, bone and joint	Mild/moderate	400 every 12 h
Any of the above in patients with creatinine clearance <30 ml/min	Any of the above	200-400 every 18 to 24 h

*As recommended by Miles, Inc, West Haven, Conn.

warfarin[74] and may also inhibit cyclosporine metabolism.[58] The concomitant use of probenecid and azlocillin decreases the clearance of ciprofloxacin.[69,75]

Dosage and Administration

Ciprofloxacin should be infused over an hour into a large vein to minimize venous irritation. Ciprofloxacin 1% sterile solution must be diluted to a final concentration of 1 to 2 mg per ml with 0.9% sodium chloride sterile solution or 5% dextrose solution. Table 2 lists the manufacturer's dosage guidelines for ciprofloxacin.

Comparative Cost

Table 3 compares the acquisition cost of intravenous ciprofloxacin at the Veterans Affairs Medical Center, San Francisco, California, with comparable doses of other parenteral antibiotics used to treat infections caused by gram-negative bacteria.

TABLE 3.—*Cost Information of Intravenous Ciprofloxacin and Other Parenteral Antibiotics*

Drug	*Dosage Regimen*	*Daily Cost, $**	*Weekly Cost, $**
Ciprofloxacin	400 mg every 12 h	48	336
Aztreonam	1 gram every 8 h	32	222
Cefotaxime sodium	1 gram every 8 h	21	147
Ceftazidime	1 gram every 8 h	31	214
Gentamicin sulfate	80 mg every 8 h	1	5
Imipenem	500 mg every 6 h	65	452
Piperacillin sodium	3 grams every 6 h	26	183
Tobramycin sulfate	80 mg every 8 h	18	127

*Costs are the cost to patients treated at the Veterans Affairs Medical Center, San Francisco, California.

Conclusions

Intravenous ciprofloxacin does not represent an important advance in the treatment of infectious diseases. With the exception of urinary tract infections, the drug is approved by the FDA only for the treatment of mild or moderate infections. Although intravenous fluoroquinolones such as ciprofloxacin may be as effective as other currently available antimicrobial agents, they have not been shown to be superior and they are expensive. In addition, because of the increasing number of reports of rapidly emerging resistance among both gram-negative and gram-positive organisms, ciprofloxacin should be reserved for the treatment of infections caused by bacteria that are resistant to standard agents including ex*ended-spectrum penicillins, the combination of trimethoprim and sulfamethoxazole, aminoglycosides, and third-generation cephalosporins. Ciprofloxacin may also be used in patients with contraindications to the aforementioned agents. Furthermore, intravenous ciprofloxacin should be reserved for patients who are unable to take oral fluoroquinolones. Ciprofloxacin should not be used for the treatment of community-acquired pneumonia or aspiration pneumonia because it has poor activity against streptococci and anaerobic bacteria. The indications for other parenteral fluoroquinolones that are likely to be available soon will be similar to those for intravenous ciprofloxacin. At this time, there is little evidence to support the use of parenteral fluoroquinolones as first-line agents for the treatment of common nosocomial or community-acquired bacterial infections.

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Epitomes

Important Advances in Clinical Medicine

Nuclear Medicine

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in nuclear medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in nuclear medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Nuclear Medicine of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Use of Thallium 201 in Tumor Evaluation

THALLOUS CHLORIDE Tl 201 is a safe, nontoxic radiopharmaceutical currently used to assess myocardial perfusion and viability. Its use has been increasing recently to detect tumors and to characterize tumor viability. This agent has been reported as being highly successful in the evaluation of brain tumors, thyroid cancer, parathyroid adenoma and carcinoma, carcinoma of the breast, primary bone tumors, soft tissue sarcomas, lymphoma, and several other tumor types.

The mechanism of ^{201}Tl uptake in tumors appears to be related to its physical similarity to potassium. It has been demonstrated that the sodium-potassium-adenosine triphosphatase membrane transport system as well as a chloride-dependent cotransport mechanism, also within the cell membrane, are the two main mechanisms of transporting thallium into the tumor cell.

Because ^{201}Tl entry into the tumor cell is dependent on active transport functions requiring intact energy-generating systems, viability studies can be done using this agent. These studies have shown thallium to be an excellent marker of viability. The success of tumor therapy can be determined by measuring the change in ^{201}Tl tumor levels following a baseline evaluation. An increase in thallium activity after therapy indicates therapeutic failure, and a reduction in thallium activity within a tumor appears to be proportional to the success of the therapeutic regimen.

Thallous chloride Tl 201 has also been used successfully in differentiating malignant from benign disorders. Most hilar or mediastinal masses within the chest that are malignant will take up substantial amounts of ^{201}Tl, but sarcoidosis appears to take up little, if any. In addition, malignant neoplasms of the breast have been shown to take up ^{201}Tl, with sensitivities approaching 96% for palpable lesions. In contrast, fibrocystic changes, which may also cause palpable breast masses, show no ^{201}Tl uptake. The use of ^{201}Tl-thallous chloride has also been successful in differentiating certain benign bone abnormalities from malignancy. A variety of tumors are particularly suited for thallium examination, including osteogenic sarcomas, Ewing's sarcoma, and malignant fibrous histiocytoma.

Thallium imaging can be started immediately after administration and the study completed in one hour. The safety of the study has been demonstrated with no serious side effects. Radiation exposure is minimal. A disadvantage associated with thallium imaging is unpredictable gastrointestinal excretion that does not allow an accurate evaluation of the abdominal area. The brain, neck, chest, axilla, breast, and inguinal areas as well as skeletal system can be easily and accurately evaluated.

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Technetium 99m-Hexamethyl Propyleneamine Oxime-Labeled Leukocytes for Diagnosis of Infection

INDIUM 111 (^{111}In) has been the primary radioisotope used to label leukocytes for detecting abscesses. Technetium 99m (^{99m}Tc), the most commonly used radioisotope in nuclear medicine, has a number of important advantages over ^{111}In. Until recently, however, there have not been effective methods for labeling leukocytes with ^{99m}Tc.

Technetium 99m-hexamethyl propyleneamine oxime ([^{99m}Tc]HMPAO) is a new radiopharmaceutical agent commonly used in brain imaging as a marker of cerebral blood flow. The complex is small, neutral, and lipophilic, allowing it to readily cross the intact blood-brain barrier. These same characteristics enable it to be used to label leukocytes. When incubated with leukocytes, the lipophilic ^{99m}Tc complex crosses the plasma membrane and changes into a more hydrophilic complex that is trapped in the cell.

In vitro and in vivo studies of leukocyte chemotaxis and function following labeling with [^{99m}Tc]HMPAO have found no evidence of cellular damage. Comparisons of [^{99m}Tc]HMPAO-labeled cells with ^{111}In-labeled leukocytes and the use of gallium citrate Ga 67 in infected patients indicate that ^{99m}Tc-labeled leukocytes are equal, and in many cases superior, to the standard radiopharmaceuticals. Sensi-

tivities as high as 92% to 100% have been found. The comparison studies are especially convincing because the same patient's leukocytes can be labeled with both ^{111}In-tropolone and [^{99m}Tc]HMPAO and then imaged simultaneously using different energy windows.

The most exciting advantage of [^{99m}Tc]HMPAO-labeled leukocytes over other labels is their ability to detect sites of infection within 30 minutes of administration. Leukocytes labeled with indium In 111 oxyquinolone detect as few as a third of cases of infections when imaged in the first 4 hours after administration; 24-hour delays are common (although some studies with ^{111}In-oxine- and ^{111}In-tropolone-labeled cells have shown a high sensitivity for infection in the first few hours after injection). The much more rapid diagnosis with [^{99m}Tc]HMPAO allows antibiotic or surgical therapy to be instituted earlier.

Leukocytes labeled with [^{99m}Tc]HMPAO have a number of other advantages as well. Unlike ^{111}In-oxine, HMPAO labeling can be done in plasma, which enhances cell viability and prevents leukocyte activation. Technetium HMPAO is a more specific granulocyte label than ^{111}In-oxine; in addition, the tag is eluted primarily from monocytes, resulting in a nearly pure granulocyte label without the need to do complicated separation techniques such as density gradient centrifugation.

Compounds containing ^{99m}Tc provide better images than those containing ^{111}In or gallium 67 because its energy is ideal for today's gamma cameras. The radiation exposure to the patient is reduced by a third to a half compared with ^{111}In-labeled cells. Technetium is always available because it is obtained from generators on site rather than being shipped in. Finally, ^{99m}Tc is considerably less expensive than the other commonly used radioisotopes.

There are some problems with [^{99m}Tc]HMPAO-labeled leukocytes, however. Bowel, biliary, and genitourinary excretion occurs. Because bowel activity does not appear until four hours after administration, early imaging will usually prevent false-positive diagnoses. Indium 111-labeled leukocytes, however, are not normally excreted into the bowel and therefore have an advantage in imaging abdominal and pelvic infections. Also, chronic infections in which leukocyte exchange is slowed may not be seen as well with [^{99m}Tc]HMPAO-leukocytes, as delays of 4 to 24 hours between administration and imaging may be required. Lower uptakes of [^{99m}Tc]HMPAO-granulocytes compared with ^{111}In-labeled leukocytes are seen in experimentally induced abscesses at 18 hours after administration due to elution of the [^{99m}Tc]HMPAO label with time. Finally, [^{99m}Tc]HMPAO labeling of leukocytes for infection imaging is not currently approved by the US Food and Drug Administration and therefore may not be available at all sites.

In summary, [^{99m}Tc]HMPAO-leukocytes are an important new technique for imaging acute infection. For more chronic infections, in suspected infection of organ systems that normally excrete [^{99m}Tc]HMPAO, or in cases where a rapid answer is not needed, ^{111}In-leukocytes or ^{67}Ga-gallium citrate may be better choices.

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Radionuclide Evaluation of Brain Death

SUCCESSFUL TRANSPLANTATION OF cadaveric organs requires the removal of organs soon after the donor's death. A prompt determination of the donor's death is necessary to avoid deterioration of the organs to be transplanted. How can it be determined when or if a critically injured, deeply comatose person on life support has died?

Since a landmark publication in 1968 by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, there have been several revisions of the criteria. The currently most widely accepted criteria were established in a report to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. These "Guidelines for the Determination of Death" state that a person with irreversible cessation of circulatory and respiratory function is dead and that a person with irreversible cessation of all functions of the entire brain, including the brain stem, is dead.

In the case of a comatose person who is mechanically ventilated, the first criterion does not apply. When the patient is determined to be neurologically dead, death can be confirmed by showing absent brain blood flow. Absent blood flow to the brain is incompatible with life. As brain tissue dies, it swells. Intracranial pressure increases, resulting in a progressive reduction of circulation to the brain. When the intracranial pressure reaches systolic pressure, circulation ceases.

A lack of brain blood flow is well shown by four-vessel contrast angiography, which is accepted as legal proof of brain death in Germany and the Scandinavian countries. Alternative methods of brain death confirmation include digital subtraction angiography and dynamic computed tomography. All of these methods require transport of the person to the imaging area.

Radionuclide cerebral angiography using diethylenetriaminepentaacetic acid (DTPA) labeled with technetium 99m has been shown to be as accurate as contrast angiography in confirming brain death. The method is noninvasive and relatively inexpensive, and, most important, it can be done at the bedside using a portable gamma camera and computer. It is quick and easy to do. Radionuclide cerebral angiography has two disadvantages. A good intravenous bolus is essential. A poor bolus or equipment malfunction during the flow study may make the study uninterpretable, in which case it would need to be repeated. Also, radionuclide cerebral angiography demonstrates the presence or absence of cerebral blood flow and does not evaluate blood flow to the cerebellum, midbrain, or medulla. Therefore, it does not meet the strict criterion of the total absence of brain blood flow.

Technetium 99m-hexamethyl propyleneamine oxime (HMPAO) is a new lipophilic agent used for cerebral perfusion imaging. It is taken up by grey and white matter in proportion to blood flow (4:1). Normally the cerebellum is visualized. Therefore, the agent can answer the question, Is there subtentorial blood flow? Imaging is not dependent on a good intravenous bolus and is not subject to fluctuations in a hospital's electrical supply. If an image is lost because of, for example, an electrical surge, it can be repeated immediately with no significant delay. Disadvantages are the relatively high cost of an HMPAO kit and its instability after preparation: The tracer should be injected within 30 minutes of

preparation. Excellent correlation with radionuclide cerebral angiography has been shown. This is likely to become the technique of choice for confirming brain death.

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Radionuclide Therapy for Thyroid Disease

ONE OF THE GOALS OF therapy is to deliver the active agent directly to the disease site and to have the rest of the body subjected to as little of the agent as possible. This principle is even more important when therapy with systemic radionuclides is considered. Iodine therapy for thyroid diseases meets this goal.

Radioiodine has a role as a primary treatment of hyperthyroidism. It also has a role in the treatment of differentiated papillary and follicular thyroid cancer. Of the hyperthyroid states, the most common is Graves' hyperthyroidism. This is ideally treated with radioiodine because the gland is diffusely involved and the uptake of radioiodine is usually greater than 50% of an administered dose. Patients of all ages can be treated. Contraindications to treatment are pregnancy and breast feeding.

Although over the years there has been debate about the appropriate therapeutic dose, some investigators try to select a dose that would bring the patient to a euthyroid state. Long-term experience, however, has dictated that this goal is often not achievable. I now advise prescribing one therapeutic dose designed to cure hyperthyroidism with the expectation that permanent hypothyroidism will occur. The patient should be counseled and recognize the need for life-long thyroid hormone replacement.

Single toxic nodules and toxic multinodular goiters can also be treated with radioiodine therapy. These conditions, in general, are somewhat more resistant to irradiation, and the prescribed dose is proportionately greater. In contrast to Graves' disease where the thyroid becomes impalpable after the administration of sodium iodide I 131, nodular goiters treated with radioiodine often are still palpable and the patient is rendered euthyroid. The incidence of posttreatment hypothyroidism is lower after the treatment of nodular goiters with ^{131}I-sodium iodide. Long-term follow-up has failed to show an increased risk of cancer or genetic abnormalities in the offspring of patients treated with ^{131}I-sodium iodide.

Radioiodine therapy for thyroid cancer is an adjuvant treatment that is given in selected patients after the primary lesion has been removed surgically. It is frequently used to ablate remnants of presumed normal thyroid after the operation. The exact role of this is still open to debate. It can also be used to treat functioning metastases in regional lymph nodes and in distant organs such as the lungs or bones. A preparatory whole-body scintiscan using ^{131}I shows the extent of disease. Should this treatment be considered, it is extremely important to discontinue exogenous thyroxine therapy and to demonstrate that the thyrotropin level is elevated. It is also important to ensure that large doses of exogenous iodine, in particular, radiographic contrast, are not given for several weeks before radioiodine therapy. If a dose of 30 mCi or more is prescribed, the patient should be admitted to hospital until the retained dose falls below that level. This treatment is well tolerated compared with systemic chemotherapy and external beam therapy. The long-term hazards that might be anticipated, including the occurrence of second malignant neoplasms, have not been described in several large follow-up studies.

Serious complications of radioiodine therapy such as thyroid storm and acute thyroiditis are extremely uncommon. Data published recently do not support a relationship between the occurrence of infiltrative ophthalmopathy and treatment with radioiodine.

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Diagnostic and Therapeutic Uses of Metaiodobenzylguanidine

METAIODOBENZYLGUANIDINE (MIBG), a guanethidine analogue developed as an adrenal imaging agent, shares a specific uptake and storage mechanism with norepinephrine. Since its introduction as a radiopharmaceutical, numerous studies have documented its high sensitivity (90%) and specificity (100%) for detecting pheochromocytoma and neuroblastoma. Consequently, MIBG has gained prominence not only in the diagnosis but also in the staging and posttherapeutic evaluation of these tumors. This agent also localizes in carcinoid (40%) and various other neuroendocrine tumors, but with less sensitivity.

When radiolabeled with either iodine 123 or iodine 131, MIBG normally localizes in the salivary glands, heart, liver, and urinary bladder with occasional uptake in lacrimal glands, normal adrenal glands, and colon. Because bone uptake is not expected in the absence of tumor involvement, osseous metastases can be easily identified.

There are several instances in which the normal biodistribution of MIBG is altered. The use of interfering medications such as tricyclic antidepressants, phenothiazine, labetalol, decongestants, and cocaine may result in a nondiagnostic or falsely negative study. These medications should be discontinued at least seven days before obtaining an MIBG scan.

Metaiodobenzylguanidine scans are indicated in several conditions. If a mass is present, an MIBG scan can indicate whether it is of neuroectodermal origin. This can be useful in hypertensive adults with incidentally discovered adrenal masses on computed tomography scans. Also, because 10% to 30% of pheochromocytomas are multiple, or extra-adrenal, these can be detected, ensuring a good surgical result. Finally, because of the occasional histologic confusion over "small blue cell" neoplasms in children, MIBG scanning can be crucial in making a diagnosis of neuroblastoma.

Compounds comprising MIBG labeled with ^{131}I and, more recently, ^{125}I are under investigation as parenteral radiotherapeutic agents to be used in advanced cases of both pheochromocytoma and neuroblastoma. Initial results

worldwide in about 100 patients indicate a 30% partial response rate of fair durability and a few complete responses. This is of particular importance in neuroblastoma, one of the most common solid tumors of infancy and childhood, in which widespread disease has a dismal long-term prognosis. In fact, ^{125}I- and ^{131}I-MIBG offer one of the few new therapeutic strategies available for this lethal cancer.

Although the availability of MIBG has been limited in the United States, there are many institutions currently doing diagnostic studies. Centers involved in the evaluation of MIBG as a systemic radiotherapeutic agent are less numerous. The approval of MIBG by the US Food and Drug Administration, anticipated sometime this year, should increase availability. In the interim, in view of the diagnostic benefits afforded, clinicians should not hesitate to request MIBG scans and refer to another center, if necessary.

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Alerts, Notices, and Case Reports

Chronic Atypical Seizure Disorder and Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism

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PSEUDOHYPOPARATHYROIDISM is a genetic form of hypoparathyroidism that results from end-organ resistance to the action of parathyroid hormone (PTH). Hypocalcemia is responsible for many of the clinical features and potential adverse sequelae of this syndrome. We report the case of a patient with pseudohypoparathyroidism type Ib in whom the failure to suspect the presence of severe hypocalcemia delayed the diagnosis despite a history of atypical seizure disorder since childhood and the development of bilateral cataracts in early adulthood.

Report of a Case

The patient, a 27-year-old African-American man with a history of seizures since early childhood, was seen because of muscle twitching and increasing seizure frequency. Significant findings on examination were widely spaced teeth with a marbled appearance, hyperirritability with a strongly positive Chvostek's sign, and mild cognitive impairment. The rest of the findings, including neurologic, were within normal limits. He was 170 cm (67 in) tall and weighed 78 kg (172 lb). Features of Albright's hereditary osteodystrophy were not present. A typical "seizure" was observed, involving pronounced stiffening of all extremities and a coarse tremor without incontinence or loss of consciousness.

His medical history included transient postnatal apneic episodes and notably delayed motor and cognitive developmental milestones. He was considered to have mild mental retardation. At age 11 "spells" developed, often beginning with leg pain followed by flexion of the extremities. An electroencephalogram (EEG) demonstrated some disorganization and slowing, with no epileptiform activity. The diagnosis of convulsive disorder was made, and he was treated with phenytoin with slight improvement.

At 16 he was admitted to hospital for episodes of tingling followed by uncontrollable jerking movements of his extremities. An EEG was unremarkable, and a regimen of diazepam was prescribed with little improvement.

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At 21 he was found to have dense subcapsular cataracts bilaterally. The patient underwent three ophthalmologic procedures under general anesthesia without incident. Continued jerking movements and seizure activity led to another medical evaluation at age 27, at which time marked hypocalcemia was found. There was no family history of seizure disorder, hypocalcemia, or skeletal abnormalities.

Initial laboratory findings included a serum calcium level of 1.25 mmol per liter (5.0 mg per dl), phosphorus 2.45 mmol per liter (7.6 mg per dl), albumin 45 grams per liter (4.5 grams per dl), magnesium 0.78 mmol per liter (1.9 mg per dl), blood urea nitrogen 6.8 mmol per liter (19 mg per dl), creatinine 88.4 μmol per liter (1.0 mg per dl), glucose 5.55 mmol per liter (100 mg per dl), free thyroxine index 2.5 (normal 1.6 to 5.2), and thyroid-stimulating hormone 2.5 mU per liter. The alkaline phosphatase level was minimally elevated at 137 U per liter (normal less than 128). A serum 25-hydroxyvitamin D_2 level was 190 nmol per liter (normal 22 to 130; 78 ng per ml), 1,25-dihydroxyvitamin D_3 was 55 pmol per liter (normal 40 to 144; 23 pg per ml), and intact PTH (immunoradiometric assay) was 8.2 pmol per liter (normal 1.0 to 6.9; 77 pg per ml), with a simultaneous serum calcium level of 1.25 mmol per liter. A second PTH value was 8.1 pmol per liter (76 ng per dl), with a simultaneous calcium level of 1.55 mmol per liter (6.2 mg per dl). An x-ray film showed thickening of the skull and salt-and-pepper granularity of the calvarium, possibly consistent with hypoparathyroidism. Intracranial calcifications were not noted. No subperiosteal resorption was demonstrable on hand films. Prior dental films were unobtainable, but roots of teeth appeared normal with intact lamina dura.

An infusion of synthetic human PTH, amino acids 1 to 34, resulted in an increment in nephrogenous cyclic adenosine monophosphate (cAMP) of only 7.4 nmol per liter glomerular filtrate at 30 minutes. Expected incremental responses in normal healthy persons and hypoparathyroid patients are 937 ± 518 and $1{,}512 \pm 707$ nmol per liter glomerular filtrate, respectively.[1] No phosphaturic response occurred. A thyrotropin-releasing hormone (TRH) stimulation test was normal. The diagnosis of pseudohypoparathyroidism type Ib was made.

Treatment with 1,25-dihydroxyvitamin D_3 (calcitriol) and oral calcium supplements caused a rapid rise in the serum calcium level, which became normal within three weeks. The patient is being maintained on 100,000 IU of vitamin D_2 (ergocalciferol) per day with a serum calcium level of between 1.99 and 2.12 mmol per liter (8.0 to 8.5 mg per dl). Levels of PTH were suppressed to 4.03 pmol per liter (38 pg per ml), within the normal range. The seizures resolved on correction of the hypocalcemia and did not recur over the next 18 months despite the cessation of anticonvulsant therapy. An EEG was repeated and was within normal limits. Cognitive function improved substantially, and the patient became successfully employed.

Discussion

A recent prospective study of patients evaluated in an emergency department for newly occurring seizure activity found metabolic abnormalities in 8% of patients, with hypocalcemia in only 1.5%. The conclusion was that, with the

ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
EEG = electroencephalogram
PTH = parathyroid hormone
TRH = thyrotropin-releasing hormone

exception of serum glucose measurements, further extensive laboratory workup was unnecessary except as indicated by the history and physical examination.[2] Unfortunately, in cases of pseudohypoparathyroidism and idiopathic hypoparathyroidism, the failure to suspect the diagnosis from a history and physical examination findings is often the crux of the problem.[3] Indeed, the most common misdiagnosis in hypocalcemic patients is "idiopathic seizure disorder."

Hypocalcemia may be responsible for a broad spectrum of central nervous system manifestations including lassitude, irritability, impaired cognitive function, and poor school performance. Psychotic behavior and extrapyramidal signs may be found in patients with calcification of the basal ganglia, which occurs in about 50% of untreated patients with hypoparathyroidism and pseudohypoparathyroidism.[4] Severe symptoms include seizures and seizure-like activity that are often precipitated by stress, vomiting, or respiratory alkalosis.

Hypocalcemic seizures can range from syncopal episodes and movement disorders to typical petit mal, grand mal, or focal seizures. Anticonvulsant therapy may delay the diagnosis because both phenytoin and phenobarbital therapy may diminish or eliminate the signs and symptoms of tetany.[5] Correcting the hypocalcemia results in symptomatic improvement regardless of the seizure pattern.

Cataract formation is associated with prolonged hypocalcemia and appears to be correlated with the duration of the abnormality.[6] The mechanism remains obscure.

Type I pseudohypoparathyroidism is a heterogeneous disorder characterized by blunting of the nephrogenous cAMP and phosphaturic responses to infused PTH.[7] Patients with type Ia have Albright's hereditary osteodystrophy and diminished Gs protein activity, ascribed to specific mutations in the genes encoding the G proteins.[8] This generalized defect may result in a decreased production of cAMP[9] and can cause resistance to multiple cAMP-mediated hormones, such as TRH and gonadotropin-releasing hormone.[10] Patients with type Ib do not have Albright's hereditary osteodystrophy, and their Gs activity is normal. Instead, they exhibit specific resistance to PTH, which is thought to result from a defect in the PTH receptor.[11] Our patient lacked Albright's hereditary osteodystrophy, failed to show a cAMP response to infused PTH 1 to 34, and had a normal TRH stimulation test, suggesting a diagnosis of pseudohypoparathyroidism type Ib.

Conclusion

Hypocalcemia due to pseudohypoparathyroidism or hypoparathyroidism may occur in the context of a vague or misleading history and in the absence of typical physical stigmata.[12] Given the potentially subtle manifestations and long-term morbidity from a delayed diagnosis, as evidenced in this patient, we suggest that all patients with presumptive seizure activity or premature cataracts be screened for hypocalcemia.

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Hypokalemia as a Cause of Tetany

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TETANY IS A condition characterized by sustained muscular contraction that often occurs in the acute care setting. We report a case of classic tetany with an uncommon, though significant, etiologic mechanism that to our knowledge has not been reported in the recent literature.

Report of a Case

The patient, a 28-year-old woman, was admitted to the Cedars-Sinai Medical Center (Los Angeles, Calif) for the evaluation of anorexia, nausea, and weakness. She was a vigorous, athletic woman who was reportedly in excellent health until ten weeks before admission when fatigue, nausea, and generalized weakness developed. In the five weeks before admission, she had intermittent episodes of uncontrollable, generalized, sustained muscular spasms of her extremities and trunk lasting as long as half an hour and occurring without apparent precipitating cause. She said she had not lost consciousness and did not have incontinence or tonic-clonic activity. She had been seen as an outpatient three times and had serum potassium levels ranging from 2.1 to 2.3 mmol per liter. The patient said that she took vitamins and levothyroxine but did not use cigarettes or alcohol or abuse drugs. There was no family history of neuromuscular disease.

Physical examination revealed no abnormalities. Her pulse rate was 70 beats per minute, and blood pressure was

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115/80 mm of mercury without postural changes. A neurologic examination was specifically notable for an absent Chvostek's sign and 2+ symmetric reflexes without clonus.

Before completing the examination, the patient complained of tightness of the chest and feeling faint. She was placed supine but within minutes generalized tetany occurred with tonic contractions of both the upper and lower extremities as well as carpal and pedal spasms.

An electrocardiogram obtained an hour before the episode showed ventricular bigeminy at a rate of 80 beats per minute and a QT_c of 519 milliseconds (normal, 400). The serum potassium level at that time was 2.3 mmol per liter.

Arterial blood gas determinations on a specimen obtained during the episode showed only mild metabolic alkalosis: pH 7.48, Pco_2 42 mm of mercury, Po_2 187 mm of mercury, and HCO_3 31 while the patient was breathing 3 liters of oxygen.

An intravenous line was established, and 15 mEq of potassium chloride was administered over 30 minutes under close cardiac monitoring; prompt muscle relaxation occurred. An electrocardiogram recorded during the episode showed normal sinus rhythm at a rate of 95 beats per minute with acute P-wave pulmonale. No ectopy was noted. Within half an hour after completion of the potassium infusion, spontaneous tetany occurred again and again responded promptly and completely to the intravenous administration of 15 mEq of potassium chloride.

Laboratory studies of blood specimens obtained during tetany yielded the following results: sodium 145, chloride 86, and carbon dioxide 35 mmol per liter; calcium 2.37 mmol per liter (9.5 mg per dl); magnesium 0.74 mmol per liter (1.8 mg per dl); phosphate 1.32 mmol per liter (4.1 mg per dl); blood urea nitrogen 7.50 mmol per liter (21 mg per dl); creatinine 88 μmol per liter (1.0 mg per dl); albumin 48 grams per liter (4.8 mg per dl); and creatine kinase 40 units per liter.

The patient was transferred to the intensive care unit where 135 mEq of potassium chloride was administered intravenously together with 60 mEq of the oral form over the next 12 hours. She continued to have spontaneous cramping of her hands and feet; this resolved with normalization of the serum potassium level. She remained clinically stable without subsequent episodes of cramping but complained of aching muscles. Serum electrolytes measured the morning after potassium repletion were as follows: sodium 139, chloride 102, potassium 3.5, and carbon dioxide 29 mmol per liter. An electrocardiogram showed resolution of the P-wave abnormality. Thyroid function tests revealed an adjusted thyroxine level of 57 nmol per liter (4.4 μg per dl; normal, 65 to 168 nmol per liter) and triiodothyronine radioimmunoassay of less than 0.30 (30%). Urine potassium excretion was 18 mmol per 24 hours in a volume of 1,290 ml. A workup in the ensuing months revealed that her profound hypokalemia was due to a surreptitious ingestion of diuretics, and she was referred for appropriate therapy.

Discussion

This case clearly demonstrates an interesting and possibly harmful consequence of potassium deficiency and hypokalemia. Because potassium is stored largely in the intracellular space, serum levels often poorly reflect total body stores and may, in fact, correlate poorly with clinical symptoms. By the time serum potassium values fall to less than 3.0 mmol per liter, severe losses have already occurred, leaving a large total body deficit. This patient, in fact, required approximately 180 mEq (intravenous and oral replacement minus measured urinary losses) of potassium chloride to raise the serum potassium level from 2.3 to 3.5 mmol per liter during the first hospital day. The total body deficit, however, may well have exceeded this figure because a return to normal of serum potassium levels probably reflects repletion of total body potassium.

The differential diagnosis of hypokalemia in a previously healthy young woman is extensive. The decreases in serum potassium levels of the magnitude seen in this patient are most commonly due to absolute total body deficits of potassium resulting from gastrointestinal or renal losses, either intrinsic or iatrogenic.[1] The diuretic abuse ultimately discovered in this patient has been seen with increasing frequency as a cause of hypokalemia of this degree and explains such a major electrolyte derangement.[2]

Common effects of hypokalemia are electrocardiographic changes including prominent U waves and conduction abnormalities such as those seen in this patient, evidenced by a prolonged QT interval (reflecting QU duration) and myocardial irritability with a tendency toward atrial and ventricular arrhythmias. The mechanism for the striking P-wave abnormalities seen in this patient is unclear but may be related to acute changes in thoracic compliance due to sustained contraction of the chest wall muscle. These effects may lead to life-threatening arrhythmias and may be potentiated by the presence of cardiac glycosides or hypercalcemia by their antagonistic effects on the myocardium.[3] This potentiation of hypokalemia by hypercalcemia, which has an antagonistic effect on the Purkinje system, becomes important in patients with tetany.[3] This patient did show ventricular ectopy that resolved during her hospital course and that was therefore thought to be attributable to the hypokalemia because further workup failed to reveal other organic-based cardiac disorders.

Neuromuscular abnormalities associated with hypokalemia are commonly reported to include malaise, fatigability, myalgias, and weakness leading to paralysis.[4] Although it seems paradoxic that tetany (representing neuromuscular irritability) would appear at a time when hypokalemia would be expected to mask tetany precipitated by other factors, references to this phenomenon are found in standard texts.[3,5] The validity of this observation is clear, however. Early observers made the clinical connection between hypokalemia and muscular irritability, but their observations were often confounded by associated abnormalities in pH and other electrolytes.[5-9] Subsequent experiments in animals confirmed the clinical impression,[10] and Fourman in 1954 provided fairly concrete experimental support in a human model by demonstrating latent and unmistakable tetany in two subjects rendered hypokalemic while pH, magnesium, and calcium levels had been maintained in near-normal balance.[11,12]

The case reported here provides additional support for the ability of isolated hypokalemia to provoke tetany. That the diagnosis of tetany was correct is evident by the nature of this patient's posturing (carpal and pedal spasm), which is a striking and characteristic feature of tetany and helps to exclude other similar abnormalities that result in cramps.[13] Measurements of serum electrolytes were repeated on several occasions, and although mild metabolic alkalosis was noted and may have contributed to the neuromuscular irritability, profound hypokalemia was the most notable abnormality. In

addition, vigorous replacement of potassium alone resulted in prompt and complete resolution of symptoms.

The mechanism by which this paradoxic effect occurs is subject to speculation and is often clouded in the literature by references to what are probably secondary effects. Specifically, tetany has been frequently reported in patients with potassium repletion presumably due to the unmasking of the effects of concurrent calcium depletion.[3,14,15]

Attempts to explain how hypokalemia could provoke tetany are purely speculative, and our understanding of the process is confounded by the complexity of the interactions of the various ions in different tissues. It is likely, for instance, that although extracellular values would suggest an isolated profound depletion in the total body stores of potassium, the intracellular ratios of sodium, calcium, and potassium or intracellular-to-extracellular ratios of these ions are not truly reflected in serum values and are contributing to the appearance of tetany. It has been shown that with a reduction of potassium stores, intracellular sodium rises at times to inappropriately high levels in excess of what is needed simply to compensate for potassium losses.[11] Similarly, from the Nernst equation ($E_m = 67.5 \times \log K_i^+/K_o^+$, where E_m is the transmembrane voltage, K_i^+ is the intracellular potassium, and K_o^+ is the extracellular potassium), it would be expected that in the presence of pure hypokalemia, cells would hyperpolarize and become more stable. It has been found, however, that potassium balance is based on a delicate relationship between absolute intracellular and extracellular gradients for potassium and potassium conductance, and severe decreases in extracellular fluid potassium lead to depolarization experimentally. It has been shown in myocardial cells, for example, that as potassium falls to less than 2.7 mmol per liter, resting potentials actually increase due to a marked fall in the potassium conductance.[3] Similar phenomena in other muscles may well lead to what would appear to be a paradoxic instability and irritability of cellular membranes.

The occurrence of tetany may also be due in part to the differential effects of hypokalemia on muscular versus peripheral nervous tissues. It has been demonstrated that cramps may result from abnormalities involving any structure from the central cerebral and cerebellar structures to the individual muscle fibers.[13] Although muscular weakness leading to flaccidity is the usual occurrence, if potassium effects on nervous tissue dominate and cause nervous irritability, tetany may, in fact, be the prominent finding. This could explain the occurrence of tetany in the presence of muscular weakness and could corroborate the frequent finding of latent tetany in previously reported cases.[8]

Finally, it is interesting to speculate why, in the presence of a common albeit severe metabolic derangement, this patient had rather unusual symptoms. Perhaps her normal serum calcium level contributed to her symptoms. Ordinarily, patients with such severe hypokalemia have hypomagnesemia and, as a consequence, hypocalcemia. It is possible that the vitamins this patient ingested contained calcium, magnesium, or both. In addition, she had mildly abnormal findings on thyroid function tests. Although the derangement was not severe, it is of interest that both hyperthyroid and hypothyroid disorders have been associated with cramping.[15]

Despite the paucity of information available regarding hypokalemia as a specific cause of tetany, its clinical consequences are clear. Hypokalemia occurs with significantly greater frequency in the usual adult population than do abnormalities of other electrolytes that cause tetany. Furthermore, treatment errors resulting from incorrect empiric therapy could have devastating consequences because of the potentiation of other concurrent electrolyte abnormalities. The patient in this report had, in addition to neuromuscular abnormalities, electrocardiographic evidence of pronounced hypokalemic effects on the cardiac conduction system. Administering calcium with its antagonistic effects on the myocardium would be expected to further worsen this situation, with potentially castastrophic consequences.

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Current Management of Diabetic Retinopathy

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DIABETIC RETINOPATHY is the leading cause of blindness in the United States in persons younger than 60 years. The Diabetic Retinopathy Study demonstrated that photocoagulation therapy is of benefit in preserving vision in patients with the more severe proliferative stages of diabetic retinopathy. Recent data compiled by the Early Treatment Diabetic Retinopathy Study (ETDRS), a National Eye Institute-supported multicenter study, showed that focal photocoagulation therapy can reduce the risk of further vision loss in diabetic patients with clinically significant macular edema. This study also showed that aspirin therapy neither prevents the development of high-risk proliferative retinopathy nor in-

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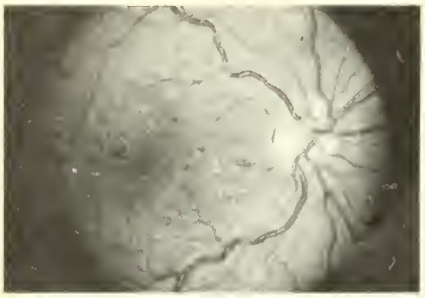

Figure 1.—Nonproliferative (background) diabetic retinopathy is manifested by the presence of scattered microaneurysms, retinal hemorrhages, and macular edema with formation of hard exudates.

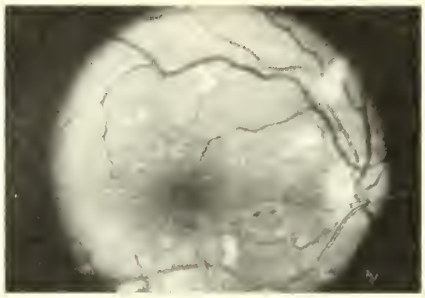

Figure 2.—Preproliferative diabetic retinopathy is shown, with multiple cotton-wool spots that represent infarcts of the nerve fiber layer.

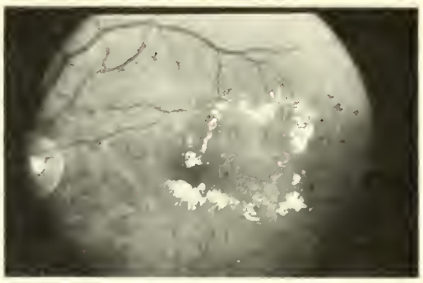

Figure 3.—This eye shows the presence of clinically significant macular edema with a circinate ring of hard exudate.

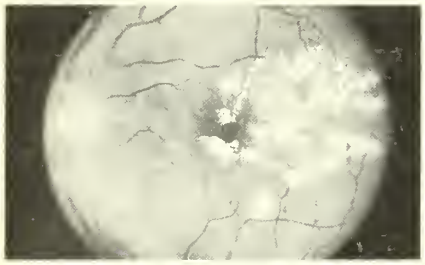

Figure 4.—The same eye as depicted in Figure 3 is shown immediately after focal photocoagulation therapy for clinically significant macular edema.

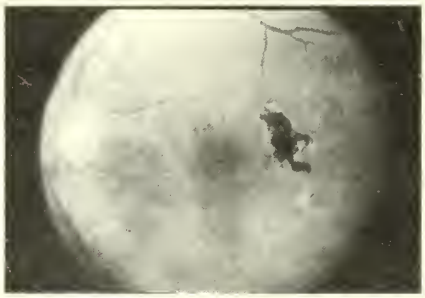

Figure 5.—The same eye as depicted in Figures 3 and 4 is shown a year after focal photocoagulation therapy. Note the resolution of the ring of hard exudate.

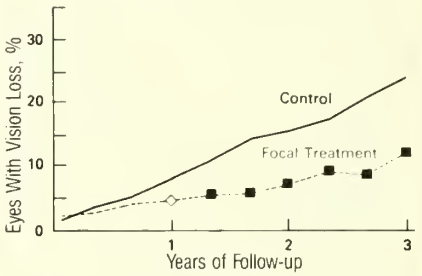

Figure 6.—Focal photocoagulation treatment of clinically significant macular edema reduces the risk of vision loss by more than 50% when compared with untreated control eyes.

creases the risk of hemorrhage into the vitreous body. I review these findings and describe a new project, the goal of which is to eliminate preventable blindness from diabetes by the year 2000.

The successful management of diabetic retinopathy is based on the early recognition of fundus abnormalities, careful follow-up, and prompt treatment. The ocular manifestations of diabetes mellitus comprise the same microvascular abnormalities that are found in other organs. The obstruction and leakage of retinal capillaries are the primary basis for the natural history of this disorder. Capillary closure and leakage result in early fundus changes referred to as nonproliferative (or background) retinopathy. The acceleration of these capillary abnormalities and the progression of ischemia eventually affect adjacent arterioles, resulting in arteriolar closure and a clinical disorder called preproliferative retinopathy. These changes indicate the potential for a rapid progression of the retinopathy. As the nonperfusion worsens, a vasoproliferative factor is thought to be released from the ischemic retina. This diffusible substance induces the growth of new abnormal blood vessels, a process referred to as neovascularization. These new vessels herald the third, and final, stage of proliferative retinopathy. This cycle of capillary closure, ischemia, and neovascularization spreads throughout the retina. The management of diabetic retinopathy is based on interrupting this cycle at each clinical stage.

Nonproliferative (Background) Diabetic Retinopathy

Nonproliferative (background) retinopathy is seen in 25% of all persons with diabetes mellitus, and its prevalence has been shown to be directly related to the duration of diabetes.[1] Patients who have had diabetes for 15 years or more have a 60% incidence of retinopathy. Nonproliferative retinopathy is the result of capillary closure and leakage. The underlying mechanism for this change is not known. Endothelial changes (thickening of the basement membrane and degeneration of the pericytes) have been demonstrated,[2] and hemodynamic abnormalities (erythrocyte and platelet aggregation) have been observed.[3] The patient may be asymptomatic, but some patients may experience vision loss due to macular edema, which is discussed later. Examination of the fundus reveals the presence of numerous microaneurysms—tiny red dots within the retina that represent saccular capillary outpouchings resulting from a nonspecific response to ischemia. These microaneurysms leak plasma constituents that can later impinge on foveal photoreceptors and result in loss of vision. Also seen are retinal hemorrhages, which may be deep (dot and blot) or superficial (flame shaped) within the retina (Figure 1).

Treatment

The management of nonproliferative retinopathy is based on maximal medical control of the diabetes. The effect of blood glucose control on the progression of the retinopathy remains controversial. There is accumulating evidence, however, that both the rate and the severity of retinal changes are favorably influenced by controlling blood glucose levels.[4] Another important part of the management of nonproliferative retinopathy is frequent (every four to six months) examinations of the fundus.[5] It has been shown that the rate of microaneurysmal formation correlates with the rate of progression of the retinopathy. Photographing the fundus is an excellent way of documenting these early changes.

Preproliferative Diabetic Retinopathy

As the microvascular changes of capillary closure and leakage progress, ischemia impinges on the walls of larger vessels, the retinal arterioles. Damage to these vessels results in larger areas of nonperfusion and leakage of blood or

plasma constituents through the defective endothelium. Arteriolar ischemia manifests as a cotton-wool spot, an infarct of the nerve fiber layer of the retina. Bleeding from a damaged vessel is seen as a blot hemorrhage, and the leakage of serum lipoproteins results in a deposition of hard exudates as the fluid is reabsorbed. The hallmark of preproliferative retinopathy is the presence of multiple cotton-wool spots, blot hemorrhages, and venous beading (Figure 2).

With progression of the retinopathy, there is continued leakage from microaneurysms and defective small vessels. Fluid then accumulates within the retina, producing retinal thickening that results in a clinical disorder known as macular edema (Figure 3). When this occurs within the central fovea, cellular distortion may lead to vision loss. The impairment that results from the accumulation of fluid may be reversible, but the damage from chronic leakage and the resultant deposition of hard exudate is permanent. Leakage that produces retinal thickening within, or threatening, the central macula has been called clinically significant macular edema by the ETDRS.

Treatment

The introduction and refinement of laser or photocoagulation therapy for diabetic retinopathy have dramatically changed the treatment and morbidity of this disorder. The primary indication for laser therapy in nonproliferative and preproliferative diabetic retinopathy is clinically significant macular edema. The ETDRS, a randomized controlled clinical trial, demonstrated that photocoagulation therapy for clinically significant diabetic macular edema substantially reduces the risk of vision loss.[6] Photocoagulation spots are applied directly to leaking microaneurysms or in a grid pattern to areas of diffuse leakage in a treatment known as focal photocoagulation (Figures 4 and 5). The ETDRS data showed that such treatment reduces the risk of vision loss by more than 50% (Figure 6). Laser therapy also increases the chance of visual improvement and decreases the frequency of persistent macular edema. The results of the study demonstrated that laser therapy is a safe procedure to undergo, although it may be accompanied by some, usually minor, side effects. Of particular note is that the benefits of treatment occur regardless of the level of vision acuity at the time of treatment. As a result, even diabetic persons with normal vision may have macular edema that should be considered for photocoagulation therapy.

The ETDRS also studied the use of aspirin to determine whether or not it was effective in altering the course of diabetic retinopathy. The results indicated that a dosage of 650 mg per day did not prevent the development of high-risk proliferative retinopathy. In addition, aspirin therapy did not increase the risk of vitreous hemorrhage and overall had no effect on vision. These results indicate that there is no reason for persons with diabetes to avoid taking aspirin in these doses when it is needed for the treatment of other disorders.

Proliferative Diabetic Retinopathy

The proliferative stage of diabetic retinopathy is characterized by the growth of abnormal new vessels and fibrous tissue in response to retinal ischemia. These neovascular vessels may arise from the optic disc and from the retinal vasculature. They appear as delicate lacy fronds of elevated vessels (Figure 7). Unlike normal retinal arteries and veins, these vessels leak fluorescein dye profusely during fluorescein angiography (Figure 8). These proliferative new vessels are also abnormal because of their propensity to bleed into the vitreous cavity and thereby obscure vision. This prolifer-

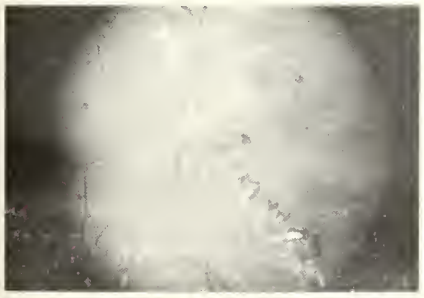

Figure 7.—Proliferative diabetic retinopathy is shown, as manifested by the proliferation of new vessels and fibrous tissue known as retinal neovascularization.

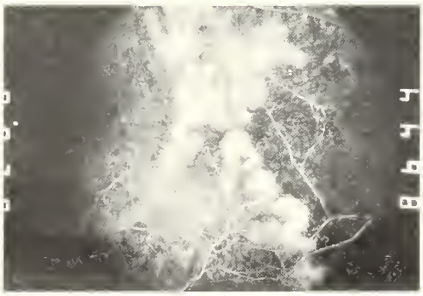

Figure 8.—A fluorescein angiogram of the same eye as depicted in Figure 7 shows the presence of fluorescein dye leakage **(white areas)** from the fronds of retinal neovascularization.

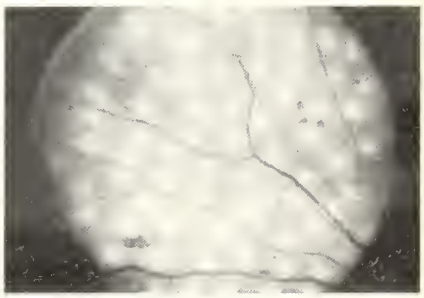

Figure 9.—Panretinal photocoagulation treatment consists of applying a scatter pattern of laser burns to the peripheral retina.

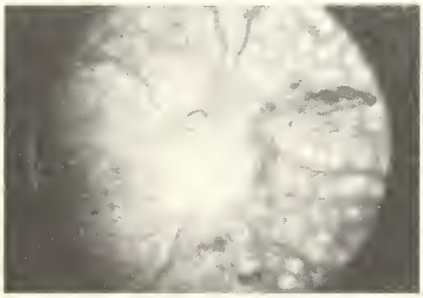

Figure 10.—Proliferative diabetic retinopathy is shown, as manifested by the proliferation of new vessels on the optic disc, referred to as disc neovascularization. Note preretinal hemorrhages and laser scars nasal **(right of photo)** to the disc.

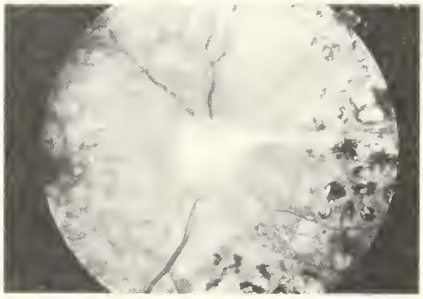

Figure 11.—The same eye as in Figure 10 shows regression of the disc neovascularization into a fibroglial strand after panretinal photocoagulation therapy.

ation of fibrous and vascular tissue may also form firm adhesions at the interface between the retina and vitreous body. As the vitreous undergoes further changes over time, traction on the underlying retina can occur, resulting in a tractional retinal detachment.

Treatment

The proliferative stage of diabetic retinopathy is initially managed by laser photocoagulation. The large areas of nonperfusion that result from arteriolar closure are thought to release a vasoproliferative factor that stimulates neovascularization. The laser is used to ablate the ischemic retina, thereby preventing release of the vasoactive substance. The technique for the application of laser spots to the entire peripheral retina is called panretinal photocoagulation (Figure 9). This form of laser therapy helps to prevent further growth of neovascularization and has been shown to induce regression of established new vessels (Figures 10 and 11).[7] Nevertheless, some patients may still suffer a vitreous hemorrhage. Most of these hemorrhages clear spontaneously over a period of weeks to months, thereby allowing the application of additional laser therapy. In a patient whose hemorrhage has not cleared after several months, a pars plana vitrectomy may be indicated to remove the blood from the vitreous cavity, thereby improving vision and enabling the necessary laser treatments.[8] When a traction retinal detachment complicates proliferative diabetic retinopathy, it may become necessary to excise the tractional fibrovascular adhesions that are responsible for the retinal detachment. Advances in surgical instrumentation also enable the application of intraocular laser photocoagulation during the operation.

Summary

Diabetic retinopathy progresses through three distinct stages. A rational approach to management is based on an understanding of the pathophysiology of each stage.

Based on the results of national multicentered clinical trials of laser photocoagulation and other treatments, advances in our understanding of the pathogenesis and treatment can now make a dramatic impact on blindness in the diabetic population:

- Panretinal laser photocoagulation treatment can reduce the risk of vision loss from high-risk proliferative diabetic retinopathy by at least 50%.
- Laser photocoagulation treatment of clinically significant diabetic macular edema can reduce the risk of vision loss by more than 50%.
- Vitrectomy can restore useful vision to some patients with severe diabetic retinopathy and vitreous hemorrhage with or without an accompanying traction retinal detachment.

Diabetes 2000 is a new project sponsored by the American Academy of Ophthalmology, the goal of which is to eliminate preventable blindness from diabetes by the year 2000. As its name implies, Diabetes 2000 will be a long-term project aimed at a specific disease—diabetic retinopathy and its complications. It will provide the latest research findings to ophthalmologists and primary care physicians as the first priority, followed by the education of patients and the general public. Recent advances and treatment guidelines for the medical and surgical treatment of diabetic eye disease will be emphasized through the continuing education of ophthalmologists, other physicians, and allied health professionals. In later phases, educational programs for diabetic persons and the public will be developed. Ultimately, improved access of diabetic patients to ophthalmologic care and a close working relationship between ophthalmologists and primary care physicians will ensure the early detection of diabetic retinopathy and the timely delivery of state-of-the-art treatments.

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Commentary

Global Health Leadership
A Continuing US Challenge

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Presented in part at the Annual Meeting of the Institute of Medicine, Washington, DC, October 14, 1991.

My original intent was to describe the United States' role in global (read "foreign," principally Third World) public health.* Even brief reflection suggests the myopic cast of this traditional formulation. Most global problems are exactly that: affecting even our own society in real and direct ways, particularly in remote, underserved, rural areas and decaying inner cities. Serious problems may be more prevalent in but are not limited to developing countries. Furthermore, these are problems of health; they are "public" only in the sense that society needs to recognize their existence and collectively invest in their solution, whether this requires more biomedical research, a new and more effective health care delivery system, or nutrition education.

Global Health Priorities

The single overarching global health priority is maximizing quality years of life at a cost society can afford. The operative terms are "quality years," not just "life," and *can* afford, not merely being "willing" to afford.

Major global (universal) health issues include, among others, the following:

- Tobacco and other substance abuse;
- Environmental pollution;
- Infectious pandemics, including the acquired immunodeficiency syndrome (AIDS);
- Population growth; and
- Women's health.

Central to them all are the organization and use of health resources, from basic and applied research through prevention and cure. No country is entirely satisfied with its health system. There is no country in which all disease that could be prevented is being prevented or where services and care are not rationed (only whether it is spread more or less evenly across economic and ethnic strata). In the United Kingdom's National Health Service, for example, patients queue two to three years for the "elective" removal of a blinding cataract, a cataract that can be removed the same day in the private sector. Every country is casting about for a better solution. If there is a single mission uniquely within the purview of public health, it is the rational allocation of health resources.

Global health priorities also include issues that are nearly universal, involving the poorer four fifths of the world's population. The most immediate priority is closing the gap between potential health, available from the judicious application of existing, appropriate technology, and the present state of unnecessary ill health.

The poorest 30 countries suffer nationwide infant mortality as high as 172 per 1,000 live births, compared with less than 10 per 1,000 in the most fortunate 30, and a life expectancy as low as 42 years, compared with over 75 years.[1] That gap largely reflects the consequences of poor individual and collective hygiene, malnutrition, and the failure to prevent and manage childhood infections. The gap is not fixed by poverty or a lack of sophisticated curative technology. There is a strong correlation between a country's gross national product (GNP) and the life expectancy of its citizens (Figure 1).[2] Most gains in life expectancy, however, are achieved within the first $1,000 GNP. A number of poor but determined countries have narrowed their health gap even as their income gap has widened.[1] China, with a per capita GNP of only $300, has a life expectancy of 70 years; Costa Rica and Jamaica, with less than a tenth our per capita GNP, share with us a 75-year life expectancy (Table 1). Sri Lanka, with a per capita GNP of only $400, has a lower infant and under-5 mortality than sections of Washington, DC. It is clearly not a matter of how much is spent but *how* it is spent.

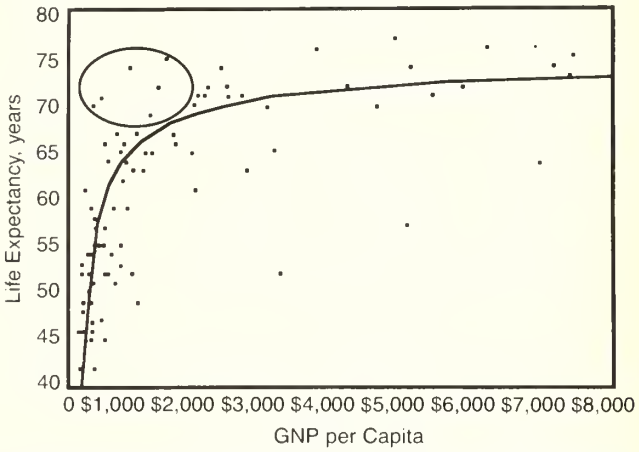

Figure 1.—Life expectancy is graphed against the per capita gross national product (GNP) for different countries around the world. Countries circled in the upper left-hand side have achieved relatively long life expectancy at relatively low levels of per capita GNP (redrawn from UNICEF data[2]).

Much of the improvement in health can be traced to other,

*See also "Eight Years and Counting—What Can Americans Do?" by A. Velji, page 84 of this issue.

(Sommer A: Global health leadership—A continuing US challenge. West J Med 1992 Jul; 157:71-73)

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TABLE 1.—*Infant Mortality and Life Expectancy in Relation to Gross National Product (GNP)*

Country	GNP, $US	Infant Mortality, per 1,000 live births	Life Expectancy at Birth, years
China	290	31	70
Jamaica	940	18	74
Costa Rica	1,600	18	75
United States	18,500	10	75

structural changes. A reasonable argument can be made that the coming of the railroad, which made possible the movement of food from surplus to deficit areas, had as great an effect on health in India as did the introduction of western medicine. In many cultures there is a direct correlation between the level of literacy, particularly of women, and childhood mortality. We should not forget that measles mortality declined dramatically in the United States long before there was a measles vaccine (Figure 2), and tuberculosis virtually disappeared long before the introduction of effective chemotherapy.

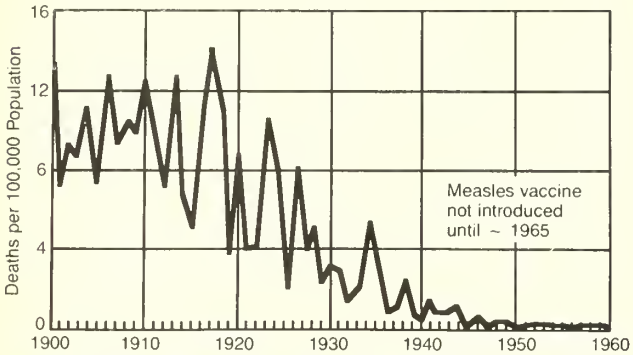

Figure 2.—The graph shows the death rates for measles in the United States before the introduction of the measles vaccine.

Organizing Public Health

How should public health organize to meet these challenges at home and abroad? By recognizing the centrality of its mission and the need to leverage effects by working closely with other health professions, by strengthening the competence of public health professionals here and abroad, and by being proactive in developing and implementing scientifically sound health policies.

Traditional boundaries limit our vision and impact. The interface between public health and medicine should become virtually seamless. "Public" and "private," "health" and "medicine," "preventive" and "curative" are artificial and divisive barriers. All countries, including the United States, are converging on a health care system that is very much public. All curative services are meant to prevent something, whether it is death prevented by cardioversion in a tertiary care emergency department, or earlier in the disease process, a change in life-style meant to prevent the development of coronary artery disease in the first place. Who is responsible for clinical trials, technology assessment, or quality assurance: the clinician who measures individual outcomes, the epidemiologist who designed the study, or the statistician who analyzed the results?

Public health is not a profession in the traditional sense of possessing a common body of knowledge. Rather, its practitioners, from many professional backgrounds, are distinguished by their common agenda: to maximize health through a scientifically based, efficient, effective, and equitable use of resources. Public health is also distinguished by the breadth of its view, from the root cause of a problem through its prevention and cure. It is no accident that the scientific symposium celebrating the 75th anniversary of the founding of the Johns Hopkins School of Hygiene and Public Health is entitled "From Cell to Society." As a thoughtful public health professional expressed it, "typhoid fever is not, as some clinicians seem to believe, simply a manifestation of chloramphenicol deficiency" (Adetokunbo O. Lucas, oral communication, May 1991).

Modern public health requires the orchestrated collaboration of a wide variety of specialists possessing a common public health orientation. At times these will include varying permutations and combinations of clinicians, epidemiologists, engineers, basic and applied researchers of every hue, and front-line field workers delivering the messages, vaccines, micronutrients, condoms, and care.

If effective public health emanates from the collective input of diverse specialists, we must reorient our academic agenda. While there will always be a need for MPH generalists, as there is for family practitioners, new leadership for practicing public health professionals is needed. This will require a Flexnerian revolution, producing leaders versed in a specific public health specialty, steeped in independent analytic thought, possessing a public health orientation, and having at least rudimentary exposure to biotechnology and to sick people. It positively frightens me to think that health care legislation is being written by MPH graduates who may never have cared for a sick patient. A modern engineer does not design a new car or plane without having first traveled in an existing model.

Finally, the "new" public health, both academic and professional, must be more willing than ever to translate research results into scientifically based policy initiatives and, where necessary, challenge the more egregious political pressures hindering reform. US society has transformed its use of tobacco products. This has been a health triumph of the first order. But official US aid and trade policies conspire to export the problem to developing countries. We share this common cause with our colleagues overseas.

Role of the United States

Although it ill-behooves us to preach a rational use of health resources given our dismal record in this regard, the United States is otherwise uniquely qualified to provide leadership in responding to international health issues: through training, training, and more training; through basic laboratory research; and by supporting—intellectually and financially—those who return abroad, thereby creating and sustaining productive and effective indigenous public health proficiency and local health awareness.

The American capacity for training public health professionals for academic and programmatic leadership is unrivaled. By themselves, our 24 schools of public health provide the wide diversity of disciplines in which specialists need to be trained.

Given the severely constrained resources of most developing countries, the obstacles our graduates face on returning home require all the problem-solving capability they can muster. The ability to recognize, define, and attack a problem is far more important to future success than is the rote

memory of public health facts. The road to the world's most successful coordinated health project, eradicating smallpox, was littered with discarded solutions: Mass vaccination failed to reach those who most needed it and was supplanted by surveillance and containment, which established an effective *cordon sanitaire* around infective cases; and just when vaccine availability threatened to become a bottleneck, introduction of the highly efficient bifurcated needle effectively quadrupled the reach of the vaccine supply.[3]

A public health professional cannot function efficiently in isolation. Effectiveness requires a critical mass of professionals. US policy should encourage the training of a multidisciplinary, complementary group of public health professionals from each region. In turn, they should seek opportunities to work with like-minded personnel from their local ministries of health and academic institutions. Collaboration among health agencies, government organizations, and academic institutions is invaluable for developing local political commitment.

In addition to training, this country has unsurpassed facilities for conducting basic laboratory research that can overcome old and new obstacles. Developing countries rarely provide hospitable environments for sophisticated molecular biology. On the other hand, developing countries represent unsurpassed field laboratories for identifying major obstacles to attaining health, for determining the effectiveness of new biologic agents, and for conducting essential applied research.[2] It is a two-way street: New therapeutic agents for AIDS, and possibly an effective vaccine, are likely to issue from research laboratories of wealthier industrialized countries, but the epidemiology and natural history of AIDS are being foretold from field studies in Africa. Contributions are sometimes circular: John Black Grant, trained at the then-new Hopkins School of Hygiene and Public Health, spent the next 15 years working in China, where he inspired people like C. C. Chen to develop and refine community-based primary health care,[4] a model that might be brought back with good effect to help solve the health crises of our own rural areas and inner cities.

Field needs and laboratory research drive one another. The Expanded Programme for Immunization is an attempt to immunize the world's children and thereby prevent millions of unnecessary deaths and disabilities annually. Despite having attained its goal of vaccinating 80% of the world's children against six major childhood diseases, available vaccines require injections, cold chains, and multiple booster shots—practical obstacles to the most effective, sustainable result. But the infrastructure capable of providing vaccines to young children has stimulated a new initiative, based on modern immunology and recombinant DNA technology, to produce a children's vaccine that is meant to provide prolonged immunity against a host of agents and from a single oral administration.

Foreign graduates of US institutions provide a skilled group of professionals with whom to collaborate. Such North-South dialogue enriches us all. American faculty and students gain hands-on experience with Third World problems and bring critical technologic bottlenecks back to the US for laboratory study. Our Third World colleagues gain fresh insight and stimulation that help maintain and enhance their skills, contribute to their health professional interest and expertise, and thereby strengthen their ability to conduct essential operational research. They also add to their international recognition and their local credibility. Indonesian scientists with whom I began collaborating on vitamin A deficiency research and control more than a decade ago now hold major health research and policy leadership positions, charting Indonesia's future and bringing invaluable experience to international advisory committees.

Conclusion

The great global health priority is to maximize quality years of life for all. This requires attacking universal problems and the nearly universal health gap of developing countries—and neglected rural and inner-city populations of the western world—through appropriate research and the organization of resources in the most imaginative, effective, efficient, and equitable way. Public health disciplines and the public health approach, strongly linked to other professions, are central to sustained success.

The United States is uniquely blessed with institutions and organized intellectual resources for training the academic and professional health leadership needed to chart rational directions and create much-needed political will. Flexnerian academic reform is critical to create a more vigorous and rigorous science-based professional public health environment at home and abroad. US collaboration, intellectual and financial, is essential to the global maturation of public health capacity and effectiveness, in both the academic and professional arenas.

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Commentary

Scientific Medicine, Social Ills, and Child Health

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It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, . . .

A Tale of Two Cities
CHARLES DICKENS

Dickens was referring to the last quarter of the 18th century when he wrote these words, but he might just as well have been talking about the last decades of the 20th century. These are, in many ways, the best of times in the biologic sciences as new horizons open with startling rapidity. But if in the future we look back on these times as the halcyon days of biologic science, we must also concede that it is among the worst of times for children in this country. First, more and more children in the United States are realizing less and less of their potential for productive and happy lives, and this during an increasingly competitive era. Second, because children are thwarted in reaching their potential, our very social system is threatened. We espouse a political philosophy of equal opportunity, and, indeed, the economic and social stability of our democracy depends on a critical mass of our citizens believing in and realizing their potential. Yet today, for significant numbers of children, the opportunity to fulfill their potential is being compromised by inadequate health care, insufficient parental nurturing, and ineffective education. Poverty is the common thread in the patchwork of services we use to cover these children.

Most physicians caring for children do not need to be persuaded about the important relationship between low family income and increased childhood morbidity. But what has this got to do with scientific medicine? Some would say that today's scientifically educated physicians cannot prevent or treat the nation's social ills, that physicians cannot prevent or treat poverty. Others might add that these are certainly issues for all of us as citizens, but hardly the special province of physicians. Research today is more than a full-time job. Providing medical care for those children who come to our offices, community clinics, and hospitals is more than a full-time job. And, of course, teaching responsibilities are added on to these activities.

I think this point of view is wrong. Francis Weld Peabody stated it most succinctly: "The secret of the care of the patient is in caring for the patient." I think that scientific physicians and physician scientists have a special responsibility to be informed, to be concerned, and to do something about the issues of poverty. This responsibility is greater than that shared by all citizens. Why do I say this? Because the relationship between health and poverty, which is a marker for many social ills, invokes two principles that are fundamental to the mission of scientific medicine. One is altruism. The other is an understanding of the intimate interaction between the health of humans and their environment. Not to address these issues as physicians is a renunciation of the Hippocratic oath. Not to address these issues while we care for children and investigate disease is unscientific.

The first concept, altruism, is a substantial part of the motivation behind most physicians' choosing a career in medicine. It should be central to medical education and treated explicitly, but most often it is not. I'm not talking about some paternalistic "noblesse oblige" but literally of altruism, the principle of putting the interest of others before self-interest.

I'm not going to spend much time on this principle, except to note that it presents a special problem in our time for all who claim to be advocates for children. And this problem arises because of the popularity and acceptance of the "market" philosophy within the health care system, including academic medical centers. The market philosophy argues that medical services are like most other goods and services and therefore should be distributed by market forces differentially to those who can pay for them. This idea denigrates the altruism principle and, because of the dire implications for those who do not receive many needed medical services, conflicts with our basic national commitment to equal opportunity. Health services for the most part are unlike other goods and services distributed in the marketplace because the consequences of not being able to obtain many health services subsequently deprives a person of a fair opportunity to compete for other goods and services in life. Indeed, it may deprive a person of life itself. In addition, if health care is not available, there are substantial untoward effects on society in general and future generations as well as untoward effects on the ill patient.

As I mentioned, however, altruism is not the only reason physician scientists and scientific physicians must take primary responsibility for addressing the poverty-related social ills that are so central to most of the health issues and disease problems of children. This responsibility is also inseparable from the scientific mission. It is unscientific to ignore the relationship between disease processes and the social and economic environment of patients.

For most human ailments, understanding the interaction between the specific pathobiology of human afflictions and

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the family and community environments in which diseased persons live is central to curing illness and relieving suffering. This is an example of the larger truth that the functioning of a living organism is fundamentally characterized by the interdependency of the organism and its environment at least as much as by its DNA. An appreciation of this interaction makes it unscientific not to address those factors in the external milieu of a child that contribute to illness or to the inability to grow and develop in an optimal way. The mission of medicine is to deal with what Dr Barondess has characterized as "ailing humans in disarray," not merely a narrowly defined abnormality in biology called a disease. To do otherwise would be as unscientific as failing to consider the complexity of genetic, cellular, and systemic factors in the internal milieu of a child that contribute to the enormous variation in the clinical manifestations of a point mutation in the genome.

These comments are not intended to deprecate the enormous contribution being made by the systematic application of the inductive experimental approach of attempting to disprove hypotheses in vitro that has been central to advances in molecular biology and physics. Rather, comparable scientific approaches should be applied to investigating the interactions between children and their macro or community environment by those physician scientists with the talent, imagination, and courage to undertake clinical investigation of these issues with the methodologies of epidemiology, biostatistics, decision analysis, and psychology and with the technologies of molecular biology.

Understanding and addressing the interaction between the pathobiology of the human organism and the community environment is fundamental to defining the nature of health problems and the ways in which scientific physicians and physician scientists can best fulfill their responsibilities to ailing persons. The problems of AIDS and intrauterine cocaine and alcohol exposure are dramatic contemporary examples of this. But there are many more. The environment of poverty or its consequences, so relevant to these disorders, is also a causative factor or significant determinant of morbidity and mortality in the majority of disorders included in any textbook of pediatrics ranging from inborn errors of metabolism to failure to thrive.

Preliminary to deciding how to address this interaction, it is important to understand some of the social anatomy and pathophysiology of poverty in this "worst of times" for children. I'm going to highlight some of what is known about these matters.

First, the definition of poverty in this country is based on a few 30-year-old studies determining the average cost of a minimally adequate diet for an adult, estimating that a third of income was spent on food, and inflating these expenditures by the cost-of-living index. Thus, a family of three must have an annual income of less than $10,000 to be considered poor. This Dickensian formula is hard to reconcile with current studies indicating that some low-income families spend more than 70% of their income on housing to avoid homelessness.

A broad demographic and social perspective is needed to understand the poverty statistics as they relate to children in the United States. Those younger than 20 now represent less than a third of the population. About 16% of these children are African American. A wave of younger children is now moving through the population. This will peak at ages 5 or 6 in about 1995, to be followed by an adolescent peak in 2005. This has obvious implications for child abuse, accidents, substance abuse, AIDS, and crime.

Perhaps more important, the proportion of children in the population has decreased dramatically, and, overall, this trend continues. Comparing children to adults over 65, we went from a ratio of 10:1 at the turn of the century to a ratio of 2+:1 by 1988. In addition, children of African-American and various Hispanic and Asian backgrounds are making up an increasing proportion of the total. Further, the proportion of households of reproductive-age adults without children has increased significantly in more recent years. It went from 20% in 1960 to 35% in 1986.

These changes have an important corollary in our workforce. In 1940 there were 17 workers for each retiree. Now there are two to three workers per retiree, and one of these is likely to come from one of the minority groups just mentioned.

There is another major demographic workforce issue related to children and poverty. It relates to the important role of mothers in the workforce outside the home. Women represent a major part of the growth in the workforce. It is projected that more than 60% of the net growth in employment through the turn of the 21st century will be by women. Currently 58% of women with children work outside the home. Since 1978, for all age cohorts of children the proportion of mothers employed outside the home has been increasing. This phenomenon is even more pronounced for single women and particularly white women with younger children. Further, many children no longer live in families with two biologic parents.

These changes are the tip of an iceberg of changing family dynamics, of affectionate relationships, of a sense of responsibility and respect, and of changing activities and behavior. The basic values that children acquire, their motivation, their sense of self-esteem and identity, and their personalities will be in large part determined by what goes on in these and other changed family units.

A recent national household survey has suggested worrisome correlations with some of these changes. A significantly lower (less than half) incidence of developmental, learning, and behavioral problems was reported by two-biologic-parent families compared with all the other family units such as single parents, parent and stepparent, and so forth.

The epidemiology of poverty among today's children and families should be viewed against the background of these demographic changes. Nearly 40% of those living in poverty are now children, although children are less than 30% of our population. African Americans and Hispanics who will make up a large proportion of our future workforce are two to three times more likely than white children to grow up in poverty. Children of single-parent African-American families, which means mostly single-mother families, are at greatest risk of growing up in poverty, which is easy to understand because the average income of all women heads of households, white and black, is less than $17,000 per year, or less than half of that of households headed by men.

What is often not appreciated is that two thirds of the children living in poverty are white non-Hispanic children. Further, more than half of poor children live in families where one parent is working in a full-time job most of the time. White two-parent families with one, or more than one, working parent are the fastest-growing group joining the ranks of those who live in poverty and those who are near-

poor (defined as those within 200% of the poverty line). These families are working hard but not making it.

The distribution of total family income reveals the basic problem. The poorest 20% of families have a tenth the income of the richest 20%. In terms of income per year, over the past decade the wealthiest 20% of families have had an average $9,000 increase in real income and the poorest 40% of families have lost real income. This is not just a matter of a shift in benefit programs away from children in poor and near-poor families, although this has happened. It is more importantly a result of the fall in wages due to the decreased number of manufacturing jobs and increased international business competition. Closely tied to a perpetuation of this problem in the years to come is a mismatch of the skills required for employment and the skills possessed by children entering the workforce.

The changes in the infrastructure of the business community in this country have also had a disproportionate effect on the economic well-being of families of children who do not live in poverty. Effective income is dramatically less in such households. The more children there are, the lower the family income.

Finally, what do these demographic changes and poverty statistics mean for the health of children? The most obvious effect relates to the affordability of health care. Poor people cannot buy health insurance and do not have the jobs that offer it. Medicaid is often inadequate and does not cover many of the poor. Current data on adults indicate a significant correlation between poor health status and inadequate insurance. More limited data on children suggest a similar relationship. About 14% of adults and 17% of children do not have any health insurance. For all ages, the uninsured range from 10% in the non-Hispanic white population to 37% for Mexican Americans, the least-insured group. If we assume that medicaid-insured and partially insured children have inadequate coverage compared to what most of us have for our own children, about 40% of children do not have adequate health insurance.

Again, it is important to keep a critical perspective about who is not insured, to investigate why they are uninsured, and to propose interventions that are most likely to improve the situation. The growth of working poor families, those in which one of two parents is working full-time but his or her income is only 25% above the poverty line, doubled in the last decade from 10.7% to 21.8%. When we look at insurance coverage for those two-parent families within 200% of the poverty line ($20,000 income or less for a family of three) where only one parent is working full-time, the change in health insurance coverage over the past decade is striking. The number of these families that became uninsured doubled as the private insurance coverage fell 39%, despite a 30% increase in public insurance. There are, of course, other effects of poverty in addition to the issue of insurance, such as poor nutrition, increased toxic exposures, and a lack of adequate preventive services.

These changes in health insurance coverage, in demography, in the economic circumstances of children, and in family dynamics are major determinants of the environmental side of the interaction between the environment and human biology that defines many of the illnesses of childhood that physicians have a responsibility to care for and investigate. I have presented this synopsis of poverty and closely intertwined social trends because understanding the interaction between the environment of poverty and children is central to fulfilling our responsibility of providing scientific and humane care to sick children, preventing illness, and facilitating growth and development. I hope that out of such understanding will come the will to act to effect strategies that will mitigate these "worst of times."

What should we as physicians and as citizens do? It is about time we join the rest of the civilized developed world and guarantee children in every state in this country the legal right to adequate health, social, and educational services and the resources necessary to ensure a healthy transition from childhood to productive adult citizenship, independent of the capacity and will of their parents. Specifically, health insurance for children should be made an entitlement, similar to Medicare, not dependent on whether a child's parents have private or public or no health insurance. Further, because of the important scientifically established relationship between the environment and health during development, health insurance for children should be tailored to the unique developmental requirements of childhood. These include a variety of social and educational services in addition to effective preventive and therapeutic medical services. Society should not attempt to substitute for the nurture and good judgment of responsible parents. Neither should the community abrogate its responsibility to ensure an opportunity for the next generation to achieve its potential solely to protect the autonomy of a family that does not provide such an opportunity.

It is easy to rationalize that the social determinants of illness are too complex and beyond our ability to control for us to focus our individual professional attention, resources, and energies on them. I think they are no more complex and beyond our control than the translation of the human genome project into the prevention or treatment of most major genetic illnesses within the same time-frame.

To return to Charles Dickens, it is up to us whether this will be the best of times, the worst of times, an age of wisdom, or an age of foolishness. We truly have an opportunity and the responsibility to do a far better thing than we have done up to now as a profession. For the most part, we know what is needed and we know how to do what is needed to make and implement sound public policy. We also have the tools to acquire additional knowledge where it is needed. It is easy to blame others for the lack of will to address the problems, but it is we who must also exercise this will in our medical centers, in our communities, and nationally. It is our professional mandate. Edmund Burke observed more than 200 years ago: "The only thing necessary for the triumph of evil is for good men [and good women] to do nothing."

This truth still holds.

Playing the Cost-Containment Game

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In the midst of today's era of "cost containment," physicians are expected to play a major role. Many of us insist we do. After all, our actions and orders initiate the spending of some 80% of our nation's health care expenditures. But, to be successful, ought we not be familiar with the "costs" involved so that we, like consumers in the supermarket, can be "price conscious" as we go about our daily business? Just what evidence is there that we are adequately informed about costs to be sure we get heard?

In 1975 Skipper and colleagues reported that as medical students evolve into physicians and as physicians gain experience, they become ever more accurate in their estimates of medical costs—diagnostic tests, drugs, procedures, and so forth.[1,2] Being a professional skeptic, I replicated their study in December 1976 and did so annually through 1987, for a total of 11 years. The process was simple: A survey form was distributed to all attendees at the Children's Hospital and Medical Center (Seattle, Washington) Grand Rounds, and all were implored to fill in the blanks with their best "guesstimates" of the costs of ten common hospital services. These included chest x-ray, neonatal intensive care daily charges, and throat culture; the specific items remained constant over the decade. Respondents also indicated their medical staff status—attending, resident, intern, fellow, or medical student. I then tallied the data, computing separate means for each of the ten items for each of the groups and the percentage of the responses that fell within ±25% of the actual costs at the time of the actual study—again, by item and by respondent group. Each January, I reported back to the attendees the results—along with the actual costs involved—and drew considerable interest in the process. Moreover, I was fortunate in conducting this study as three "interventions" were introduced into our hospital operation: distributing copies of patients' bills to all members of the medical team involved in the care; posting an itemized price list on each of the clinical units; and adapting that price list to a user-friendly computer made available on each unit as the avenue of communication with the laboratory, radiology, medical records, and others. Naturally my null hypothesis was that none of these innovations would affect accuracy rates each subsequent December and that experience per se would also be of no consequence in enhancing the accuracy of cost estimates. Imagine my distress as the data that came in bore out those null hypotheses! Let me explain.

Each year some 90 attendees completed each exercise, with at least 20 in each of the separate groups. Simply put, the mean guesstimates were not that far off targets, being within 10% of actual costs, but, consistently, less than a third of the respondents' guesses fell within Skipper and associates' gold standard of ±25% of the actual cost. At no time during the ten years of the detailed study were the medical students' mean estimates significantly different from those of the other respondent groups, nor did their "spreads" (variance) differ from those of other groups. Moreover, as far as I could tell, each of the innovations was without notable effect—the means and spreads showed no significant changes during the years after they were introduced.

So much for the bad news. There may also be good news. When the means of all the respondents in any given year were totaled and compared with the totals of the actual costs involved, the differences averaged *less than 5%* for each of the ten years. Even more notable was the observation that over the decade, while the annual percentage increment of the "medical care component" of the federal consumer price index was 9.0% per year, that of the respondents' guesstimates was also 9.0%—81.4% total for the former and 81.0% total for the latter!—suggesting that though the respondents were ignorant of the cost of specific items, they were surprisingly conscious of both global costs and inflation.[3(p483)]

"So what? Is there any take-home message applicable to today's cost-containment game?" you might ask. I think so. Admittedly our samples were small and subject to bias; surely it would have been preferable had all the specialties been represented. But our data were remarkably consistent, with no internal conflicts over the span of the study. Nonetheless, replication would be highly desirable. In the meantime, let's all agree that we are, in fact, surprisingly ignorant of individual cost items and that we should be wary about sharing that ignorance with patients if we do not look up actual costs before reassuring them. "Don't shoot from the mouth when it comes to costs"—or should it be "charges"?—especially as Representative John Dingell's investigations subcommittee of the House Energy and Commerce Committee has "exposed" the enormous but widely divergent markups prevalent throughout the medical care industry (M. C. Kimball and C. Havighurst, "House Panel Grills Humana," *HealthWeek,* October 21, 1991, vol 5, pp 1, 32). So, too, we need more precise information when we participate in negotiations or press conferences where we are presumed to be informed. Tierney, Ball, and others have argued that rather than push familiarity with costs per se, we would all do better to focus on "value."[4,5] In truth, because value is a function of costs and benefits, access to cost data would still be essential to establish value. As Samuel Johnson said centuries ago, "Men more frequently need be reminded rather than informed," which is surely the case with cost data. Today, with cost schedules changing almost daily, keeping up with such changes would seem mandatory if we as physicians are really

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serious when we proudly proclaim our efforts at cost containment. Without an awareness of these cost changes locally, how can individual physicians conceivably discharge any obligation to try to constrain medical cost escalation? So, too, on both the state and national levels, how can the profession profess to be making such an effort when its component organizations must be assumed to be comparably ignorant?

At this point I admit to a bit of bias and a tad of paranoia. I worry that our medical profession, individually and as a group, repeatedly finds itself in a defensive mode of trying to play catch-up on financial matters. Invariably we are forced to rely on data gathered and massaged by others. Frequently the whole process takes place well in advance of our opportunity to participate in any critical way or even to become familiar with the real meanings of the terms being used. This is hardly an ideal spot to be in, especially as the nation seems to be approaching some type of a "nationalized" health care program. Will a word to the wise be sufficient? Can, and should, we as individuals or as members of the profession do anything to rectify the situation? Or is it too late to do other than give the appearance of doing something? Our data verified that physicians as a group have a surprising global knowledge of costs and a feel for changes going on around them. Now all we need is quick and ready access to specific bits of data to flesh out our capacity to help our patients and ourselves actually win the cost-containment game. Who will take the first step to get the job done?

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* * *

ALPHABET

for Alicia

Last night I bound you to the letter A.
Your spine curving in the X-rays became
the stack of blocks I built
spelling your name, a father's wobbly trick
and hope to hold you, laughing,
to harness and frame—your first friend
among the wooden letters you used to smuggle
everywhere. (Giving you away, they bulged
like extra knees,
so we made a game where I frisked you
and guessed messages, and was always wrong.)

Last night, awakened by the stress of legs
against leather straps, I found you sleeping
with the letter A in your right hand
and the letter A in your left hand,
the moon in your window bending close
as the mirror in the doctor's headband.
Were you dreaming your name? A's
like an alligator's grin,
dots swarming from i's,
the stinging tails of l's and c's? Daughter,
our dreams are games that hold us to the earth.

THOMAS REITER©
Neptune, New Jersey

Earthquakes and the Office-Based Surgeon

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A major earthquake may strike while a surgeon is performing an operation in an office surgical facility. A sudden major fault disruption will lead to thousands of casualties and widespread destruction. Surgeons who operate in offices can help lessen havoc by careful preparation. These plans should coordinate with other disaster plans for effective triage, evacuation, and the treatment of casualties.

(Conover WA: Earthquakes and the office-based surgeon. West J Med 1992 Jul; 157:79-82)

The purpose of this article is to encourage and assist surgeons who operate in offices to prepare for a major earthquake of magnitude 7.0 or greater on the Richter scale. A brief review of the formidable nature of such an event may serve as a catalyst for this preparation.

Many unstable and treacherous seismically active fault zones and plate rifts have been mapped throughout the world. Examples of these areas located on the North American continent alone include the Alaskan archipelago; the Juan de Fuca plate along the Pacific Northwest coast; California's San Andreas fault; Utah's East Bench fault; and the extensive New Madrid, Missouri, fault zone (the scene of a series of the greatest earthquakes ever recorded in the continental United States, 1811 to 1812). Earthquakes have a capricious nature and will occur in long-dormant or unsuspected fault areas. Physicians and surgeons should become familiar with the location of their practices in reference to fault zones to evaluate their vulnerability and to develop earthquake preparedness programs.

California and the Western States

To bring the immensity of the earthquake problem in focus with increasing office-based surgical procedures, consider the following prime example of intense seismic activity.

California has experienced 5,000 earthquakes since 1769 of Richter scale magnitude 5 or greater. During the past 20 years, 19 earthquakes of magnitude 6 or greater were recorded in the Los Angeles area alone. It is highly probable that a great earthquake of a magnitude of 8 or larger will strike in the near future along the southern section of the San Andreas fault that runs east of San Bernardino and southward to the Salton Sea. Major earthquakes have occurred in this area about every 145 years; the last one occurred 135 years ago. About 3,000 deaths may occur if the "big one" strikes early in the morning, or as many as 14,000 deaths if it takes place in late afternoon; structural damages will amount to $17 billion.

Were the Newport Inglewood fault, adjacent to the San Andreas fault, to rupture again, far greater destruction would be expected than in a San Andreas quake, mostly because of the population density and unstable soil. The Federal Emergency Management Agency estimates a late afternoon major quake would result in 23,000 dead, 91,000 severely injured, and a property loss of $69 billion. Based on 1988 estimates, 34% of the available hospital beds in Los Angeles and Orange counties would be lost because of damage.

In northern California, the central section of the San Andreas fault, along with two parallel active branches, the Hayward and Calaveras faults, forms an intimidating ellipse that encloses the San Francisco Bay region and the immediate inland and southern land areas of high-density population as far south as the cities of Watsonville and Hollister. The great San Francisco quake of magnitude 8.2 on April 18, 1906, and the recent Loma Prieta quake of magnitude 7.1 on October 17, 1989, are two examples of the more devastating quake disasters in this area.

Geologists estimate that there is a 40% or more chance of a magnitude 7 earthquake on the Hayward fault in the next 30 years and more than a 67% chance for such an earthquake in the San Francisco Bay Area. The Loma Prieta quake, if anything, has increased the chances. Scientists are currently concerned about the seismic activity of the converging Hayward and Calaveras faults in the San Jose area and in the vicinity of Hollister to the south.

Two other areas covering Washington-Oregon and Utah have notable treacherous fault zones. The first and greater lies along the eastern edge of the Juan de Fuca tectonic plate just off the coastline of the Pacific Northwest. The fault runs 750 miles from Cape Mendocino, California, to Vancouver Island, British Columbia. The strain in the rocks of the fault is calculated to be so great that it could release at any time in a probable series of tremendous quakes of magnitude 9 or greater. The second dangerous unstable fault is the East Bench fault that runs directly through Salt Lake City, Utah. The Mississippi Valley, with widespread fault patterns, is another area of possible recurring devastation. Great earthquakes occurred in the New Madrid, Missouri, area in 1811 and in Charleston, South Carolina, in 1886.

Surgeons in these areas should take note and prepare accordingly, for there is no room for apathy, denial, or underestimating the risks. The disruption of communications, electric and water power, and transportation will be immediate. Chaos and confusion at every level of governmental and private sectors within the perimeter of the quake will likely ensue.

Earthquake Scenario for Office Surgeons

Some surgical procedures can be done in an office-based operating room. These surgical facilities are designed to meet the rigid standards of hospitals, emergency departments, and outpatient surgical units. They are sophisticated and efficient.

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Unlike their general surgery colleagues, whose work is done in settings with extensive emergency facilities and personnel for back-up, office-based surgeons are solely responsible for anticipating *all* emergencies in the surgical suite and in the office in general. This should include earthquake disasters, especially in high-probability areas.

The violent force of a magnitude 7.5 quake may come when a surgeon is performing an operative procedure in an office setting on the fifth floor of a medical building with the patient under heavy sedation or a general anesthetic. The shaking may continue for as long as one minute. Frequent aftershocks may occur; some may be greater than the first. Utilities, communication, and transportation will be instantly disrupted. A third of hospital beds and many medical personnel will be lost in moments. It may take 72 hours or more to sort out casualties and return utilities and transportation to a manageable level.

If surgeons have prepared for such an event, they and their staffs should respond with some sensibility. If there has been no planning, the surgical area will be in a deplorable state; surgeon, staff, and patient could become casualties.

Earthquake Preparedness of Office Surgical Facilities

In preparing an office to meet a major earthquake, the surgeon must consider the before, during, and immediate aftermath. All three phases must mesh with an office-building plan.

Before the Event

The surgeon must concede that a serious quake will happen sooner or later and be willing to do something about it *now*. The location of earthquake faults in relationship to the medical office building should be determined. The subsurface on which the office building rests should be defined. Buildings erected on soft alluvial or sandy landfill areas or over areas with high water tables will suffer the most structural damage. Seismic waves are amplified in these areas, causing liquefaction of the soil and weakening of foundations, leading to irreparable structural damage, a disruption of building contents, and loss of life. If the ground and building are structurally stable, the physician must realize that this does not assure stability of the building contents.

Important safety measures include using simple mechanical devices to secure and stabilize furniture, equipment, and supplies to prevent in-office casualties from falling and flying objects and to reduce the possibility of expensive losses. In addition, a written protocol should be provided for personnel response to the quake with an assurance for practice sessions and timely updating.

The "disaster response program" for the office building should provide a system for the safe evacuation of tenants and patients, efficient triage (using the START program), and treatment and holding stations for the evacuation of casualties to functioning hospital facilities. These facilities are to be supported by a communications team that is in contact with local emergency network systems by amateur radio. These positions can most likely be filled by soliciting and organizing volunteers from within the medical building.

Gurneys and wheelchairs will not be able to be used on elevators because of power loss. Fire, police, and ambulance services, limited at best, will be spread thin and may be unavailable for two or three days. Arrange for fire-fighting instruction, the use of litters for nonambulatory patients, and access to emergency medical supplies. Refer to the section, "Guidelines for Office Personnel."

During the Event

Operating surgeons will have at least two reactions during uncontrollable earth movements: to *survive* and to *protect* the patient. A dead surgeon and staff are useless. The outcome will largely depend on the surgical team being prepared and being as calm as the situation will allow. Rehearsing beforehand and recognizing the need for instant improvisation are most likely to lead to good judgment and sensible actions.

Open wounds and instruments must be covered. By leaning over the operating table, the surgeon and scrub nurse may be able to stabilize and protect the patient from falling debris. A face may be quickly shielded by a Mayo stand. Airway conduits and intravenous lines will have to be kept in place; anesthesia personnel and the circulating nurse can help with this. Intravenous poles will roll or topple unless they are attached to the operating table. Other suggestions are listed under the heading, "Safeguarding an Office Surgical Facility."

After the Event

After the initial shaking stops, further violent aftershocks may follow and dislodge already-weakened overhead fixtures. Consider moving the operating tables, along with the anesthesia unit, closer to an inside unencumbered wall. It may prove to be a safer, more sturdy supporting structure.

The operation should be completed as quickly as possible. Electrical units used for controlling small bleeding vessels will not function. This actually will be an asset, for an electric spark may cause an explosion due to possibly ruptured gas lines. Bleeding may be controlled by other measures.

By the time the patient can be safely evacuated from the office, the building preparedness measures should be in effect. A litter bearer team may have to be summoned through a floor leader for assisting in evacuating the patient. One member of the surgical team should accompany the patient to a safe holding station, well clear of the building, where ongoing "recovery" can be provided until the patient can be safely released. The patient's condition on discharge, the name of the person to whom care is transferred, and the destination should be carefully recorded. Written instructions for postoperative follow-up care should be given if possible. A packet of appropriate medication to cover the immediate postoperative period for up to three days should accompany the patient because local pharmacies and hospital supplies will be depleted or otherwise impossible to reach.

Generally speaking, the surgeons and physicians on the premises will either find their way to preassigned building preparedness stations, help as they see fit, or be assigned through the building's command or coordination center. Surgeons who have survived the crisis can also make their way to any preassigned station once immediate obligations to care for and evacuate surgical patient(s) and office personnel have been fulfilled.

The communications center will assist those who have committed their volunteer services elsewhere (schools, hospitals) to find out how practical it might be to get to those places in the event of citywide destruction, with bridges down and roads blocked, that may make it impossible to travel.

Surgeons should not be assigned to triage but rather to immediate or delayed-evacuation holding stations where their skills are required for diagnosis and supporting treatment before casualty evacuation to hospitals. Specially trained paramedic personnel are best used to do triage.

Safeguarding an Office Surgical Facility

The following suggestions may help an office surgical facility to prepare for a major earthquake. Surgeons may wish to modify, embellish, delete, or make innovative additions as deemed practicable.

- Ensure that the medical building has an earthquake preparedness plan.
- Provide an office emergency communication system because telephone lines will become overloaded or power lines will be down. Walkie-talkies, cellular telephones, or an employee designated as a "runner" can be used.
- Have an AM-FM battery-operated radio to monitor emergency broadcasting stations. Have a supply of extra batteries.
- Stabilize and tightly secure anesthesia equipment, operating table, monitors, supply bins, suction and cautery units, and defibrillators, with heavy-duty industrial-grade Velcro. Vital and expensive equipment may otherwise disconnect, fall, or crash and be rendered useless.
- Bolt large, free-standing equipment cabinets to wall studs with metal "L" brackets.
- Secure all cabinet doors and drawers with special hooks, catches, or latches to prevent spills.
- Secure large oxygen and nitrous oxide tanks by strapping them to special metal stands provided by the vendor on request.
- Have an extra-large oxygen tank on hand.
- Have available an E cylinder oxygen tank with regulator and Ambu bags to accompany patients on litters during evacuation and recovery.
- Have installed, in accordance with building codes, a small emergency generator as a backup system to provide electric power independent of the building power source. These small generators will activate the operating room light and necessary electrical equipment such as the monitors and suction unit needed to complete an operation. The generators should be tested regularly.
- A surgical head lamp powered with a belt-hinged battery pack will prove useful.
- Secure a wall-mounted, battery-powered, operating room clock with heavy-duty Velcro.
- Have more than one flashlight with extra batteries.
- Window glass may explode instantly; danger from flying glass can be reduced effectively by covering the inside of the glass panels with an acrylic safety film.

Guidelines for Office Personnel

- Assign an office "earthquake chief" and assistant chief to direct the office activities in case of a major disaster.
- Formulate a plan of action and discuss it with the office crew and floor leaders and then post it in a prominent place.
- Secure computers and typewriters with heavy-duty Velcro.
- Keep current an inventory of employees with names and telephone numbers and nearest relative. Have each employee carry a card in their wallet with the same information.
- Identify the cash box with physician's name and have a fireproof safe for accounts receivable and other important documents.
- Instruct office personnel to have a three-day supply of any medications they are taking to tide them over in a major disaster.
- Have a three-day supply of water, food, and first-aid supplies.
- Have a loud whistle or horn available in the office to signal for rescue, if necessary.
- At the instant of the earthquake, call for everyone to duck and cover for protection from flying glass and falling equipment and fixtures.
- Do not light candles; there may be a gas leak. Use flashlights instead, and keep a supply of flashlights along with extra batteries.
- Quickly and calmly inspect all rooms, including the waiting room. Have a clipboard and make appropriate notes. Calm the patients by telling them that there is an earthquake preparedness plan in action and that they will be safe by following your instructions.

When the floor leaders arrive, advise them of the following: office structural problems, serious casualties needing help, and fire. Indicate that the office is ready for evacuation and indicate to floor leaders the "all clear" when evacuation is complete.

- Do not use the telephone lines until authorized by the communications center.
- Be sure to wear shoes to protect feet from shattered glass.
- Quickly triage injured patients and employees. Tag them appropriately with standard color-coded triage tags for proper disposition. Render emergency treatment. Request a special rescue team, if necessary.
- Do not remove persons who have been killed. Properly identify them with triage tags. Report the location of victims to the floor leader and building director who, in turn, will notify the command or coordinating team. The coroner's office will arrange for removal of the body.
- Standard color-coded triage tags may be purchased from the fire department by the building preparedness leaders for distribution to the offices.

When the floor leaders indicate that your office is cleared for evacuation, be sure to lock your cash boxes (remove the keys and carry them with you), and take and guard the daily patient log book to assist the floor leaders and building director in determining the completeness of evacuation of the offices and to identify a patient who may have become an earthquake casualty.

- If there is fire and heavy smoke, crawl to the stairwell, being careful to avoid glass debris.
- Once clear of the building, do not reenter unless otherwise authorized by the command center team, as severe aftershocks may trigger additional falling debris and cause injury.
- Above all, remain calm. You think and act more clearly if you do not panic. Review the preparedness measures frequently with the entire staff, including front-office crew. Brief every new employee on the details of the office and building earthquake preparedness plans.

Conclusion

Earthquakes of major proportions are likely to strike in the foreseeable future in the western states, as well as other

densely populated, seismically high-risk areas throughout the country. Knowing the history and the potential of these devastating quakes and the capriciousness of earthquake faults should motivate everyone, including surgeons who operate in an office surgical facility, to prepare *now* to safeguard the lives and premises of their immediate concern and responsibility.

There will be little anyone can do during the shaking period, but preparation beforehand will make the during and after periods easier to cope with. Being unprepared will compound the disaster.

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* * *

ONLY HUMAN

i was glad
i had taken the time
to hold the dead man's head in my hands
and comb his hair
even though i am always afraid
combing the dead fibers
will make them fall out

and i was glad
i had rolled a towel
and placed it under his gaping jaw

and that i had arranged the crisp white sheet
smoothly and neatly
across his motionless chest

for when she asked through tear-filled eyes
if she could see him and say good-bye
all i could do was nod my head
and hope my eyes were communicating the words
wedged so snugly in my throat

LU CARTER, RN©
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Editorials

You Light Up My Life . . . and Liver
Gastroenterologic Laser Therapy in the 1990s

LASER, AN ACRONYM for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation, implies an intense, monochromatic, and readily focused light. When used in tissue, the response is dependent on a number of variables. These include not only the wavelength of the laser used but also power settings, pulse duration, repetition rate, and distance from which the laser is applied. Similar tissue changes can be generated at either low power settings applied for longer time frames or with higher power settings and short pulses, effects ultimately contingent on local tissue temperature and the concept of power density.

As reviewed elsewhere in this issue of the JOURNAL in an article by Pritikin and co-workers,[1] lasers have evolved in gastroenterologic application from simple thermal procedures used for cutting (surgical scalpel), coagulation (hemorrhage control, lesion destruction), and photoablation (tissue vaporization) to include photodynamic and photoacoustic capabilities. In this evolutionary process, original laser applications, such as hemostatic control of bleeding peptic ulcers, have largely been supplanted by portable, equally efficacious, and more cost-effective treatments. Thus, with the exception of "watermelon" antritis and colorectal bleeding from radiation telangiectasias, two widespread lesions that are most readily treated by noncontact laser application, the majority of bleeding lesions are better handled with injection therapy or other thermal techniques (heater probe, bipolar cautery).[2,3]

As noted by Pritikin and colleagues, thermal lasers have fared somewhat better in the treatment of gastrointestinal neoplasia, allowing endoluminal continuity of obstructing gastroesophageal or colorectal neoplasms and assisting in the ablation of sessile colonic polyps.[4-8] Even in the treatment of obstructing gastrointestinal cancers, however, the use of lasers is being challenged. For instance, bipolar tumor probes appear, at least in some hands, to be equally efficacious in treating circumferential tumors and can be applied more rapidly than conventional neodymium-yttrium-aluminum-garnet (Nd-YAG) laser therapy.[9] The administration of caustics such as absolute alcohol to effect tissue necrosis and slough has also been reported.[10] Finally, gastroesophageal endoprostheses, admittedly often difficult to place from both patients' and physicians' perspectives, are being reconfigured as coated, expandable wire meshes that appear to offer comparable efficacy to rigid prostheses and may be considerably less noxious to place.[11] All of these developments, as well as parallel advances in thermal laser technology to include contact tips, lateral aiming probes, and air-cooled and thus portable lasers, will continue to alter the technologic balance and the application of that technology for the foreseeable future.

Photodynamic therapy, in turn, undertaken using laser fluorescence after the intravenous administration of a photosensitizer, has yet to fulfill its promise of local tumor necrosis and ablation while leaving normal tissues unscathed.[12] Not only have normal tissues been noted to retain varying amounts of the most commonly used hematoporphyrin photosensitizing agents, but the precise timing of sensitizer injection followed by laser application remains ill defined. This is related, in part, to varying tumor vascularity among patients.

Lasers have been used to fragment stones both urologically and gastroenterologically, which facilitates the retrieval of ureteral and common bile duct stones, respectively. Our group has reported a number of in vitro studies, was the first to use in vivo therapy in choledocholithiasis, and participated in a multicenter trial in patients in whom common bile duct calculi could not be retrieved by conventional methods. Problems remain with this technology, however.[13-15] These problems include the need to ascertain the apposition of the transmitting quartz fiber directly onto the stone to minimize the risk of bile duct damage. Such assurance is possible only by passing a fiber through a miniscope, a tedious and variably expensive procedure. Accordingly, in our institution we reserve dye laser therapy for cases in which alternative treatments—mechanical lithotripsy, extracorporeal shock wave lithotripsy—are unsuccessful in effecting stone fragmentation.

What role do lasers play in the gastroenterologic practice of the 1990s? In contrast to the unrealistic patient expectations fed by Buck Rogers serials and Star Wars news coverage, current and anticipated future lasers are one of many complementary or competing technologies that have variable application in daily practice. As a thermal modality, laser therapy is a valuable tool, particularly when used in conjunction with snare cautery, for broad-based colorectal adenomas. It is one of several competing technologies in the palliation of unresectable or metastatic gastrointestinal malignancy. Lasers play a small part in the treatment of gastrointestinal bleeding and a smaller role still in the fragmentation of biliary stones. Photodynamic therapy has yet to fulfill its potential.

Despite all this, gastroenterologic lasers have evolved from a medical curiosity in the mid-1970s into a limited but definitive therapeutic tool in the 1990s. Costs to purchase, maintain, and apply; efficacy; and side-effect liability must be put into the perspective of other endotherapies to define its ultimate role in our therapeutic armamentarium.

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Eight Years and Counting—What Can Americans Do?

THE SEARCH FOR President Bush's "new world order" and the World Health Organization (WHO) agenda, "Health for All by the Year 2000," are neither theoretical nor rhetorical. In two previous articles, "International Health Beyond the Year 2000"[1] and "International Health,"[2] I reviewed the major challenges and some solutions to global health problems.

If the United States adopts global leadership in efforts to improve the health of people everywhere, 1992 could be a pivotal year.[3] Health for the "global person" could translate into "the new diplomacy"; better health could be the new lingua franca replacing the arms race and the cold war. The total US budget is about $1.5 trillion for fiscal year 1992; the WHO budget for fiscal year 1992 is only $735 million, less than the budget of the US Public Health Service's Centers for Disease Control in Atlanta, Georgia.[3] One suggestion is that US assistance to the WHO can be provided as extrabudgetary funds—a special contribution above and beyond its regular assessment of 25%.[3] President Bush and Congress may reduce the armed services budget by $50 to $100 million during the next five years. This peace-time "fallout" of extra funds could be used to improve health both at home and globally. In its new role as leader in efforts to improve the health of all people, the United States would have to put increased pressure on the European Economic Community, Japan, Taiwan, Singapore, and other economically strong nations to contribute more to the WHO's dwindling resources as AIDS, cholera, floods, drought, and earthquakes continue to wage their own wars on humanity.

Elsewhere in this issue, Alfred Sommer, MD, adroitly outlines global health priorities, including those affecting people in the United States, and emphasizes maximizing quality years of life at a cost society can afford.[4] He identifies the organization and use of health resources as the pivot. Dr Sommer emphasizes the need to maintain close communication with other health professionals who have a common agenda; he rightfully calls for eliminating the divisive barriers hindering close relationships among global health professionals. Moreover, the International Health Medical Educational Consortium (IHMEC) has also mandated reorienting medical school academic agendas to reflect society's demands and realities.[2] Dr Sommer calls for the same efforts by the schools of public health,[4] which for nearly 100 years have given top priority to the health needs of society. IHMEC task forces are currently addressing issues of clinical sites, curriculum, career track and certification, communication, and liaison in a comprehensive effort to ensure that candidates not only have health profession experience but have also "looked after sick people."

Because both dollars and human resources are scarce, we must use plain economic sense and social justice and put increased pressure on our academic health centers to return to their primary mandate of working for public and societal good.[5-7] Academic institutions must claim the "three-legged stool" of cost, access, and quality of care.[6] Those of us in public health and medical schools must care for this "stool" and ensure that it also sprouts a fourth leg of societal priorities with equity. We must become part of the "new world order" instead of reluctant players.

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Meta-analysis Redux—Steroids and Meningitis Revisited

THERE ARE MANY CLINICAL SITUATIONS for which firm therapeutic recommendations cannot be made based on existing data. Sometimes these situations can be identified by the fervor of the discussions surrounding them. Loud, data-free arguments, by necessity based on belief rather than a critical appraisal of relevant literature, frequently occur when new therapies become available or are applied to new uses and before there are enough trials to give clear answers to clinical questions. When more data become available, quieter deliberations are the rule as clinicians try to sort out what to do in the face of sometimes conflicting information from different studies.

Elsewhere in this issue, Geiman and Smith use the techniques of meta-analysis in an attempt to sort through the available data and make a recommendation concerning the use of corticosteroids as adjunctive therapy for the treatment of pediatric patients with bacterial meningitis.[1] Their excellent analysis offers a useful summary of the information available from clinical trials in this area. Their recommendations for use are somewhat firmer than I think the data allow at this time.

In the pediatric studies included in their meta-analysis,[1] early[2] and late[3] neurologic sequelae and moderate or more severe bilateral hearing loss[2] were significantly diminished by dexamethasone therapy in only one trial each. When

results of all available studies were combined, however, patients treated with dexamethasone had improved neurologic outcome at hospital discharge and at follow-up examination and less bilateral hearing loss at follow-up examination. The authors conclude that dexamethasone use in conjunction with bactericidal antimicrobial therapy is useful in reducing neurologic sequelae and hearing loss following bacterial meningitis in children, and they recommend its routine use, especially for severe disease caused by *Haemophilus influenzae*. Existing data are insufficient to allow this strong a recommendation.

Although a useful technique for summarizing data, the combining of results from several clinical studies is always open to criticism, as shown by an examination of the details of the studies included in this meta-analysis. Four of the studies[2-4] were done under the direction of a single investigator, and two were reported in a single publication.[2] While those studies were well designed and carefully reported, the evidence would be stronger if there were trials from a variety of different groups. Different antibiotics were used in the various trials. For example, medications for meningitis caused by *H influenzae* were chloramphenicol plus sodium sulfadiazine,[5] ampicillin plus chloramphenicol,[6] cefuroxime,[2,4] ceftriaxone,[2] or cefotaxime.[3] Dexamethasone doses also were not uniform in the six studies included in the pooled data. One trial was published in 1969, and the results may not have a strong relationship to medical practice in 1992. Another trial was performed in Egypt,[6] and patients in general had more advanced disease at presentation than the subjects in the other trials. The results may not be comparable to those obtained in other locales with patients with different disease severity.

It is possible that dexamethasone appears to be useful in these studies in part because of the high rates of poor outcome in the control groups. Four of the trials used a second- or third-generation cephalosporin as the antibiotic therapy for these patients with bacterial meningitis.[2-4] The placebo groups in these studies showed high rates of neurologic abnormality (29/149; 19.5%)[2-6] and hearing loss (22/157; 14%) at follow-up examination.[2-4,6] High rates of poor outcome in the control groups have the effect of increasing the measured differences in risk between treatment and control groups in a given population sample, even if the outcome in the treatment group in the study sample is no better than in a control group (not treated with dexamethasone) at another institution or from another era.

The question to be answered is not "Does dexamethasone show benefit in these trials?" but rather, "How do the rates of poor outcome in the dexamethasone-treated study patients compare with the rates of poor outcome in patients treated in other institutions with other antibiotics but without dexamethasone?" Although dexamethasone use decreases the risk of poor outcome in patients treated with cephalosporins, there may be no improvement when compared with the outcome of patients treated with ampicillin and chloramphenicol during a previous era. Pomeroy and co-workers evaluated neurologic function following bacterial meningitis in 185 patients treated with ampicillin and chloramphenicol between 1973 and 1977.[7] The mean duration of follow-up for these patients was 8.9 years.[7] Of the 185 patients, 8 (4%) had neurologic abnormalities at follow-up and 18 (10%) had persistent hearing loss.

Comparison of the rates of poor outcome in the control groups of the four cephalosporin-dexamethasone studies[2-4] with the rates reported by Pomeroy and colleagues[7] suggests that ampicillin plus chloramphenicol therapy is associated with a better neurologic outcome at follow-up examination (risk difference [RD] = −15%; 95% confidence interval [CI] −22% to −8%) and a lower risk of persistent hearing loss (RD = −4%; 95% CI −11% to 3%) than is therapy with cephalosporin antibiotics alone.

Comparing the rates of poor outcome in the treatment groups of the four cephalosporin-dexamethasone studies[2-4] with the rates reported by Pomeroy and associates suggests that the use of a second- or third-generation cephalosporin plus dexamethasone results in a lower rate of late hearing loss (RD = −6%; 95% CI −11% to −0.5%) than does therapy with ampicillin and chloramphenicol alone. There is no difference, however, in the rates of neurologic abnormality between the two series, and the risk of late neurologic sequelae actually is lower in the ampicillin-chloramphenicol–treated group (RD = 3%; 95% CI −2% to 8%).

These somewhat complex comparisons between treatment, control, and other groups of patients with bacterial meningitis are open to as much criticism as the original meta-analysis that suggested them. The point can be made, however, that the increase in inflammation associated with the use of second- and third-generation cephalosporin antibiotics alone leads to worse neurologic sequelae after treatment than the neurologic sequelae that follow the use of ampicillin or chloramphenicol alone. To make the neurologic outcome after meningitis therapy with cephalosporins as good as that after therapy with ampicillin and chloramphenicol, dexamethasone must be added to diminish the added inflammation (and associated neurologic damage) that may come from the use of rapidly bactericidal antibiotics like cefotaxime and ceftriaxone. In fact, this vigorous inflammatory response from bacterial lysis has led to the suggestion that dexamethasone should be administered before antibiotics.[3]

Since submission of the manuscript of Geiman and Smith,[1] there have been two other publications of interest on this subject.[8,9] McCracken and colleagues reported a retrospective review of 97 children in Dallas, Texas, with pneumococcal meningitis from 1984 to 1990; they showed no statistically significant differences in the neurologic or audiologic sequelae of patients treated with dexamethasone compared with those not so treated.

The Infectious Diseases Society of America in January 1992 published recommendations concerning glucocorticosteroid use in bacterial meningitis,[9] stating that there exists "moderate evidence to support a recommendation for use" of dexamethasone as adjunctive therapy for "infants and children with early *Haemophilus influenzae* meningitis." The authors also stated that because of inadequate data, they could not make recommendations for corticosteroid use in patients with meningitis caused by *Streptococcus pneumoniae*.[9]

There seem to be enough data to justify a provisional recommendation that dexamethasone be given to patients with bacterial meningitis caused by *H influenzae*, especially if a second- or third-generation cephalosporin is used for antibiotic therapy. The combination of bactericidal antibiotic (cefotaxime or ceftriaxone) and anti-inflammatory therapy probably helps reduce the risk of persistent hearing loss compared with other therapeutic options. The dose of dexamethasone used in most studies is 0.6 mg per kg per day given in

four divided doses for a total of four days. Although there are theoretical reasons[3] to suggest that giving dexamethasone before antibiotics might be beneficial, there are no clinical data proving that the use of corticosteroids before antibiotics is better than their use after antibiotics.

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Correspondence

History and Diagnosis

To the Editor: I read with some personal delight the article in the February issue by Peterson and colleagues on contributions of the history, physical examination, and laboratory investigation in making medical diagnoses.[1] In my academic university practice (which I suspect is not unlike the departmental practice at the University of Utah Wasatch Clinics in Salt Lake City), many of my patients, referred by other physicians, come in carrying large bundles of papers. Over the years, the histories contained in these "referral packets" have become shorter and shorter and the number of laboratory diagnostic studies, roentgenogram reports, computed tomography reports, magnetic resonance imaging reports, endoscopy reports, biopsy results, and so on has become greater and greater.

Because both physician-referred and self-referred patients were included in the study, I wondered how many of the former brought with them laboratory reports as part of the "history." The word "history," if my experience is any gauge, has changed over the years to include less and less of the symptoms and story of the patient and more and more of the story of their previous medical investigative adventures. If this is so, then the implication of this study as to the importance of "history" does become different, as "history" may now mean "history of my diagnostic studies."

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1. Peterson MC, Holbrook JH, Hales D, Smith NL, Staker LV: Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. West J Med 1992 Feb; 156:163-165

* * *

To the Editor: Peterson and co-workers have confirmed the primacy of the medical history in the evaluation of symptomatic patients who had laboratory investigation only when indicated.[1] Analysis of experience in our executive health program has afforded me an opportunity to assess the relative contributions of history, physical examination, and testing in mostly asymptomatic persons who, until recently, underwent a standardized testing protocol. Because this was a screening program, our review end point was not a final diagnosis but the identification of problems justifying further evaluation. That analysis showed most new discoveries were, indeed, made through the history and physical examination.

The results of 429 consecutive evaluations done over nine months were analyzed, with 40 notable new problems, including angina pectoris, leukoplakia, and prostatic nodules, found in 37 patients. Of these, 7 (18%) were found by history alone, 6 (15%) by physical examination alone, and 9 (22%) through a correlation of the history and physical examination. Of the identified problems, 14 (35%) were unexpected abnormal laboratory findings, but other studies such as radiologic procedures and pulmonary function testing had a low yield. These data underestimate the value of the history and physical examination in that certain problems such as excess weight, hypertension, and an unhealthy life-style were recorded separately and not included in this analysis. Elevated cholesterol levels were also separately reported and, had they been included in the laboratory analysis, would have increased the apparent yield of blood testing.

This analysis shows the importance of "low-tech" interventions in preventive care, just as Peterson and colleagues have shown the importance of the history in evaluating symptomatic patients.[1] Our preventive programs now emphasize history-taking and the physical examination, and standardized testing protocols have been replaced with targeted investigations.

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1. Peterson MC, Holbrook JH, Hales D, Smith NL, Staker LV: Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. West J Med 1992 Feb; 156:163-165

If Syncope, Think Long QT

To the Editor: I want to congratulate my two colleagues in pediatric cardiology for their concise and informative overviews of heart disease in children in the April issue of the journal.[1,2]

I would like to add an additional comment. Unexpected and not readily explained syncope in children or adolescents probably deserves one piece of technology: an electrocardiogram. The long QT syndrome or Romano-Ward syndrome is a cause of sudden syncope and sometimes sudden death in an adolescent. There may be nothing in the history or physical examination to suggest heart disease, but if the results of a neurologic evaluation are negative, an electrocardiogram may elicit the definitive diagnosis. Immediate referral to an expert in pediatric electrophysiology would then be indicated.

No one is anxious to increase the cost of health care, but an electrocardiogram that uncovers a case of the long QT syndrome may well be lifesaving.

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Correction

To the Editor: I am writing you regarding my epitome, "Current Concerns with Collagen for Soft Tissue Augmentation," in the February 1992 issue.[1] The original publication stated that "To date, about 100 cases of dermatomyositis, polymyositis, and lupus associated with collagen injection disease have been reported." This statement should have read, "To date, about 100 cases of alleged associated autoimmune diseases have been reported in connection with collagen use." Although dermatomyositis, polymyositis, and lupus are clearly diseases within the family of autoimmune diseases, the associated cases of supposed autoimmune diseases reported with collagen use frequently do not have well-established diagnoses. This type of nonspecific presentation fits with the epidemiologic studies that have not been able to establish a causal relationship between these two factors.

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Lessons From the Practice

Quality Medicine

ROBERT L. GOLDSTONE, MD, *Newport Beach, California*

There are many days in a physician's life when the sun is shining outside but not inside. The task of healer, involved with the intricacies of each individual hope and fear, weighs heavily on our minds at all times. The rewards and triumphs that make it all worthwhile are sometimes diminished by the lessening of the intense personal contact that is as glorious as it is difficult.

When the number of frustrations seem to be outnumbered only by the number of patients still waiting for a helping hand, my thoughts often drift to Dr DePrume. Like all young aspirants to the throne of medicine, I got my initial inspiration from a source that I remember vividly—the physician who had the small office above my father's pharmacy.

Dr DePrume's practice was different from those I had seen on television. The physician license plates that made it possible to park on New York City streets adorned not a Cadillac or a Mercedes but a well-worn Renault. The people who came to see him were not attired in suits and ties but often in clothing reflecting their multicultural backgrounds.

I watched as people came down from Dr DePrume's office to us with a prescription to be filled. As my father tended to that, I spoke to them, wondering what went on in that small office. I had seen the fancier offices in New York City. Many of the patients had been there before coming to Dr DePrume. None said they would ever turn to anyone else.

When I told my father I'd like to be just like Dr DePrume, esteemed, caring, and important, he lit up. "Terrific man." "Really a symbol." "All-cash practice—he knows what he's doing." Like many youngsters, I never really grasped medicine as a financial means. Yet Dr DePrume went home with so many boxes and odd gifts that I suspected this was far from the lucrative practice of my father's dreams. In fact, judging from the number of patients who had trouble even meeting the cost of the prescribed medication, I wondered sometimes if Dr DePrume was paid at all.

I went upstairs one fall to meet him, utterly in awe. With a waiting room full of patients, he never left until the last person was seen. He introduced me to them as a young physician in the making. I was amazed he could remember all of the names and all of the problems. I saw the looks in patients' eyes, always full of hope: So this may be the young doctor who one day will care for us.

I finished college and went to medical school, and each summer I worked in my father's pharmacy to help pay my tuition. True to form, Dr DePrume's office was always busy. The acknowledgments from the patients were the same. They always seemed privileged to be seeing him. Still tall and stately, advancing years had slowed him a bit, but his enthusiasm never dulled. As I passed through an academic residency and fellowship, I wondered how he could run such a practice in New York City. As I began publishing papers and working in hospitals with the most advanced technical equipment, I often wondered how he could be practicing "quality" medicine.

After my training, I joined a large state-of-the-art health maintenance organization (HMO). My patients slowly became more numerous. I remembered fewer names and problems without the chart. The patients seemed equally disinterested in the system. I flew back home that summer, hoping to get some inspiration from the man who seemed to have all the answers years before I knew what the questions were. I was a bit late. Dr DePrume had retired the year before. His office was now another HMO. The physicians there mechanically turned out health care. I'm sure it was excellent care, but I wondered what had happened to the faces that had looked imploringly at me those many years before.

I now realize that it is not the science or the art of medicine that is dying but the practice of it. There were dreary and cold days in the big city, but the smiles of those who were touched by Dr DePrume provided the sunshine in that office. Physicians will usually do well financially wherever they work, but that practice was far richer than either my father or I ever knew. "Quality" medicine may never be the same.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Goldstone RL: Quality medicine. West J Med 1992 Jul; 157:88)

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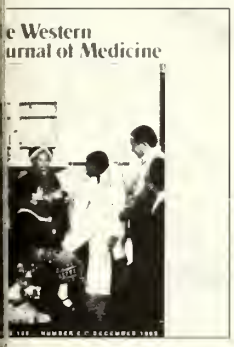

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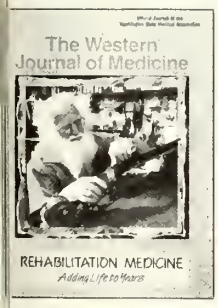

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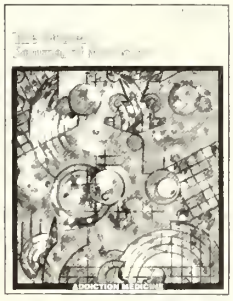

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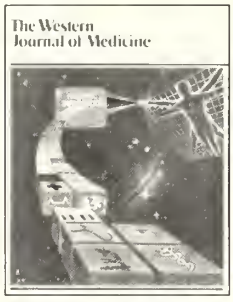

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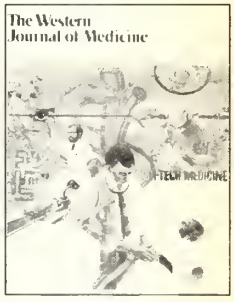

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December 14-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

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November 10-14—**VIIth International Symposium on the Biology of Vascular Cells.** Scripps Clinic and Research Foundation at Princess Resort Mission Bay, San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

NEUROLOGY

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October 23-24—**Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery and Anesthesiology.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. Contact: UCLA Division of Neurosurgery, (310) 206-0626.

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USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

OB/GYN

July 26-29—**5th Annual In Vitro Fertilization and Embryo Transfer: A Comprehensive Update—1992.** UCLA at Four Seasons Biltmore Hotel, Santa Barbara. Sun-Wed. 20.5 hrs. $400-$522. Contact: UCLA Extension.

July 29—**10th Annual Controversies in OB/GYN.** Memorial/UCI Center for Health Education at Mauna Kea, Hawaii. Wed-Sat. Contact: UCI.

October 3-4—**Ultrasound Update: 1992.** UCD at Sacramento. Sat-Sun. Contact: UCD.

December 3-5—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas. Thurs-Sat. Contact: Brenda Ram, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

OCCUPATIONAL/ENVIRONMENTAL

July 26-31—**Sports Medicine.** UCSD at San Diego Princess Resort. Sun-Fri. Contact: UCSD.

October 19-30—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. 1½ wks. 80 hrs. $1,400. Contact: UCSF.

November 2-6—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 12-18—**18th Annual Lukes Lymphoma Conference.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Sun. 25 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

October 24—**Melanoma and Pigmented Lesions.** Stanford University Medical Center at Fairchild Auditorium, Stanford. Sat. Contact: STAN.

October 26-28—**16th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, Cancer Symposium, 5665 Oberlin Dr, # 110, San Diego 92121. (619) 453-6222.

November 5-8—**Prostate Cancer.** Sutter Health at Hyatt Regency, Sacramento. Thurs-Sun. Contact: Sutter Health, (916) 733-3883.

OPHTHALMOLOGY

July 29-August 2—**Summer Institute.** American Academy of Ophthalmology at Sheraton Palace Hotel, San Francisco. Wed-Sun. $325-$500. Contact: Sarah Samuels, (415) 561-8515.

September 10-13—**Uveitis and Retinal Frontiers.** UCSF at Carmel Valley Ranch Resort. Thurs-Sun. Contact: UCSF.

October 10—**Ophthalmology Update: 1992.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

December 10-11—**Glaucoma Management.** UCSF at Ritz-Carlton, San Francisco. Thurs-Fri. Contact: UCSF.

ORTHOPEDICS

October 31—**Orthopedics Symposium.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

November 5-6—**Low Back Pain and Its Relation to the Sacroiliac Joint.** UCSD at San Diego Convention Center. Thurs-Fri. 12 hrs. $335. Contact: UCSD.

December 9-13—**Fall Symposium on Back Pain.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

PATHOLOGY

August 7-8—**Southwestern Regional Cryostat and Microscopically Controlled Surgical Workshop.** UCSD at La Jolla. Fri-Sat. 15 hrs. Contact: Daniel Gormley, MD, 412 W Carroll Dr, Ste 207, Glendora 91740. (818) 963-7684.

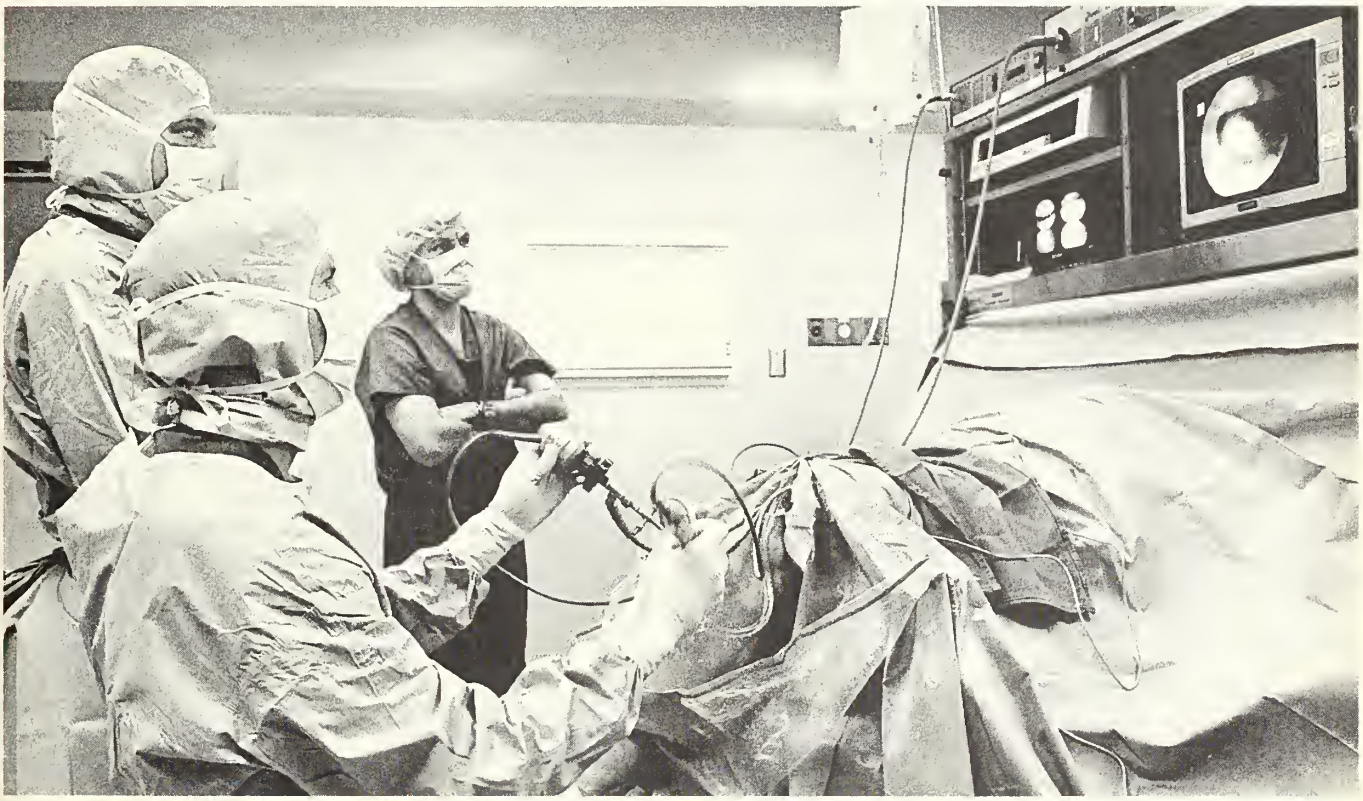
August 9-15—**12th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Mauna Lani Kohala Coast, Big Island of Hawaii. Sun-Sat. 27 hrs. $950. Contact: UCSF.

October 10—**Fine Needle Aspiration: Advanced Tutorial XXI.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

October 17—**32nd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Irvine Marriott. Sat. Contact: Sylvie Tarro, (310) 641-8152.

(Continued on Page 92)

LET ME TELL YOU ABOUT THE FIRST TIME I WAS ON TELEVISION.



As a family practice physician, Dr. Alvin Sockolov had assisted in operating room number 7 at Sutter General Hospital many times. But after re-injuring his knee, there he was, undergoing ACL surgery at the hands of Dr.

David Coward. While choosing surgery was a difficult decision, choosing Sutter General was not. "Dr. Coward prefers to operate at Sutter General," says Dr. Sockolov. "A surgeon needs special equipment, fine instruments, and a capable staff to feel comfortable. Sutter General has what physicians need for procedures to run smoothly." More orthopedic surgeries are performed at Sutter General Hospital than at any other hospital in the region. Advanced diagnostic equipment, specially trained orthopedic nurses, and a team of rehabilitation specialists all help give Sutter General a reputation that's unmatched in Northern California. In addition, educational programs, a health library, outpatient and extended care facilities provide both physicians and patients with the best resources available. "The only problem I had with Sutter General," says Dr. Sockolov, "was that when it came time to leave, I didn't want to go. Everything was top-notch." For more information about available services, call Sutter Orthopedic Center at Sutter General Hospital in Sacramento, (916) 733-8880.

Alvin Sockolov, M.D.

Sutter Orthopedic Center
SUTTER GENERAL HOSPITAL

(Continued from Page 90)

October 26-30—**Urological Pathology: Current Concepts and Recent Developments.** American Society of Clinical Pathologists at Santa Barbara. Mon-Fri. 25.5 hrs. $690. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (312) 738-1336.

PEDIATRICS

July 13-22—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

July 17-August 5—**Lactation Management Education Program.** UCSD. 1½ wks. Contact: UCSD.

August 24-26—**Pediatrics Update: 1992.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-26 & October 19-24—**Lactation Management Education Program.** UCSD at Wellstart, San Diego. Mon-Sat. Contact: UCSD.

October 19-22—**17th Annual Pediatrics for the Practitioner.** Long Beach Memorial at Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact: Eunice Larson, MD, (310) 595-3422.

PSYCHIATRY

July 17-18—**The Developing Brain: New Frontiers of Research.** UCLA at Neuropsychiatric Institute. Fri-Sat. $100-160. Contact: UCLA Extension.

July 24-28—**13th International Congress on Child and Adolescent Psychiatry: Violence and Vulnerability.** UCSF at Fairmont Hotel, Nob Hill, San Francisco. Fri-Tues. Contact: UCSF.

August 4-9—**Neuropsychiatric Aspects of Politics and Politicians.** American Academy of Family Physicians and Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Kamuela. Tues-Sun. 22.5 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

August 7-11—**The Power of the Art—Suggestive Therapeutics: An Introduction to Medical Hypnosis.** UCSD at Mission Bay Hilton, San Diego. Fri-Tues. Contact: UCSD.

November 13-15—**38th Annual Group Therapy Symposium.** UCSF at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. Contact: UCSF.

PULMONARY MEDICINE

September 17-19—**11th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $410. Contact: UCSF.

RADIOLOGY

July 17-19—**Vascular Imaging and Intervention for the '90s.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-22—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Ritz-Carlton, San Francisco. Mon-Wed. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 20-24—**Clinical Imaging for the Non-Radiologist.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Radiology for Non-Radiologists.** UCSD at Hotel del Coronado, San Diego. Thurs-Sun. 18.5 hrs. $425. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 23-26—**Diagnostic Imaging Update: Body Imaging, Mammography, MRI, Interventional.** Stanford University Medical Center at Quail Lodge, Carmel. Thurs-Sun. 10.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

July 27-August 1—**Advanced Neuro MRI—Beyond Spin Echo and Musculoskeletal MRI.** Hoag Memorial Hospital Presbyterian at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Sat. 32 hrs. $645. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

August 10-14—**Radiology & Clinical Correlation for Non-Radiologists.** UCSD at Hotel Del Coronado, San Diego. Mon-Fri. Contact: UCSD.

September 9-11—**8th Annual Sonography Update.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 12-13—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 20-23—**UCLA Digital Radiography and Image Management Networking Conference.** UCLA Medical Center at Miramar Sheraton Hotel, Santa Monica. Sun-Wed. 16 hrs. $345. Contact: UCLA.

September 21-23—**Digital Radiography and Image Management Networking.** UCLA Radiological Sciences at Miramar Sheraton Hotel, Santa Monica. Mon-Wed. 16 hrs. $345. Contact: UCLA Radiological Sciences, (310) 206-7435.

October 1-4—**Western Neuroradiological Society Annual Meeting.** Western Neuroradiological Society at Ritz-Carlton, San Francisco. Thurs-Sun. 11.5 hrs. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 24-25—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-30—**17th Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25.25 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 30-November 1—**12th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 2-6—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Mon-Fri. 15 hrs. $400. Contact: UCSD.

SURGERY

September 14-18—**What's New in Vascular Surgery: A Comprehensive Review and Update.** UCLA at Miramar Sheraton, Santa Monica. Mon-Fri. 34 hrs. $469-$625. Contact: UCLA Extension.

October 16-18—**Hip and Knee Reconstructive Surgery: 1992.** UCLA at Westin Hills Resort, Rancho Mirage. Fri-Sun. 14 hrs. $595. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. Sun-Sat. 36 hrs. $500-$995. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. 1 week. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

July 12-17—**21st Annual Summer School of Alcohol, Tobacco and Other Drugs.** UCSD. Sun-Fri. Contact: UCSD Extension.

September 24-27—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. Thurs-Sun. Contact: UCLA Extension.

October 22-25—**American Pain Society: 11th Annual Meeting.** American Pain Society at San Diego. Thurs-Sun. Contact: APS, 5700 Old Orchard Rd, Skokie, IL 60077-1057. (708) 966-5595.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 20-24—**19th Annual Renal Disease Program.** University of Colorado's CME in the Rockies at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 27-31—**16th Annual Dynamic Psychotherapy Program: Trauma, Memory and Psychotherapy.** University of Colorado's CME in the Rockies at the Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 29-31—**Management of Pediatric Diabetes in the 1990s.** University of Colorado's CME in the Rockies at Keystone. Wed-Fri. Contact: U of Colo.

(Continued on Page 93)

(Continued from Page 92)

July 30-August 1—**Update on Current Medical Ethics Issues for the Clinician.** University of Colorado's CME in the Rockies at the Given Institute, Aspen. Thurs-Sat. Contact: U of Colo.

August 3-6—**Sixth Annual Echocardiographic Symposium on 2-D and Doppler Echocardiography.** American College of Cardiology at Marriott's Mark Resort, Vail. Mon-Thurs. Contact: Margaret Sgro, (800) 257-4739 or FAX (301) 897-9745.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 21-22—**Second Annual Musculoskeletal Infection Society Meeting.** University of Colorado's CME in the Rockies at Snowmass Village, Snowmass. Fri-Sat. Contact: U of Colo.

September 10-13—**Colorado Medical Society Annual Meeting.** Copper Mountain. Contact: CMS, PO Box 17550, Denver 80217-0550.

September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

September 18-23—**Primary Care Computing.** University of Colorado's CME in the Rockies at the Given Institute, Aspen. Fri-Wed. Contact: U of Colo.

September 25-26—**Montrose Memorial Hospital Fall Clinics.** Montrose Pavilion, Montrose. Fri-Sat. Contact: N. Robert Brethouwer, DO, (303) 249-2211.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 9-13—**38th Annual Family Practice Review.** University of Colorado Health Sciences Center, Denver. Wed-Sun. Contact: U of Colo.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 22-25—**Current Concepts in General Surgery.** Hilton Hotel, Albuquerque. Wed-Sat. Contact: D. Mendoza, UNM SOM.

July 24-26—**Arrhythmia Diagnosis and Management.** Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Heather Anthony, New Mexico Heart Clinic, 1001 Coal SE, Albuquerque 87106. (505) 242-2796 or (800) 888-6642.

August 13-15—**The Crisis of Children Exposed to Drugs and Alcohol: Community Responses.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

August 15—**Transfusion Medicine: Oxygen Transport and Hemostasis.** Holiday Inn Pyramid, Albuquerque. Sat. Contact: UNM SOM.

September 7-11—**Mammography Update.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 8-9—**Critical Care Obstetrics.** Holiday Inn Pyramid, Albuquerque. Tues-Wed. Contact: UNM SOM.

September 10-12—**Perinatal Care Update.** Holiday Inn Pyramid, Albuquerque. Thurs-Sat. Contact: UNM SOM.

September 11-12—**Essentials of Health Care for the Elderly.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM SOM.

September 18-19—**New Mexico Chapter, American College of Surgeons, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Fri-Sat. Contact: William Abbott, MD, 711 Encino Pl NE, Albuquerque 87102. (505) 843-7901; or Bonnie Smith at the New Mexico Medical Society, (505) 828-0237 or (800) 748-1596.

September 26-27—**Pediatric Infectious Diseases for the '90s.** Plaza Hotel, Las Vegas. Sat-Sun. Contact: Marilyn Stark, New Mexico Chapter, American Academy of Pediatrics, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431; or George Bunch, MD, 501 7th St, Las Vegas 87701. (505) 425-3566.

October 8-11—**The American Academy of Pain Management 1992 Annual Conference.** Hyatt Regency Hotel, Albuquerque. Thurs-Sun. Contact: Janice Mohr, American Academy of Pain Management, 3600 Sisk Rd, Ste 2-D, Modesto, CA 95356. (209) 545-0754.

October 9-10—**Effective Psychotherapy: Research and Practice.** Sheraton Old Town Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

October 22-24—**Practical Orthopaedics in the Primary Care Setting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 22-24—**Infectious Disease: Issues and Challenges in Obstetrics and Gynecology.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 30-November 1—**The Emotional Life of the Infant: Clinical Applications.** Hilton Hotel, Albuquerque. Fri-Sun. Contact: UNM SOM.

November 6-7—**Update for Radiographers.** Four Seasons Quality Inn, Albuquerque. Fri-Sat. Contact: UNM SOM.

December 3-5—**American College of Physicians, New Mexico Chapter, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

December 11-12—**Trauma Update 1992.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

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July 31-August 1—**UOS Shakespearean Festival Meeting** (Sponsor: UOS). Fri-Sat. Contact UOS.

(Continued on Page 94)

(Continued from Page 93)

August 6-8—**ISLD Dental Congress** (Sponsor: UUSM). Tues-Sat. Marriott Hotel, Salt Lake City. Contact: UUSM.

September 10—**Monthly Meeting** (Sponsor: UOS). Thursday evening. Contact: UOS.

September 16-19—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 13-18—**Summer Institute of Public Health Practice.** Seattle. Mon-Fri. Contact: Northwest Center for Public Health Practice, (206) 685-3089.

July 16-18—**Diabetes Update.** Seattle. Thurs-Sat. Contact: U/W.

July 23-26—**Current & Emerging Issues in Cancer Pain.** Seattle. Thurs-Sun. Contact: U/W.

July 30-August 1—**STD Update.** Seattle. Wed-Fri. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact. Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

August 3-8—**Summer Seminar in Medical Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 7—**Pediatric Cardiology.** Seattle. Fri. Contact: Children's Hospital, (206) 526-2501.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

August 28-29—**Pediatric Orthopedics.** Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

August 28-30—**17th Annual Washington State EMS Conference.** Spokane. Fri-Sun. Contact: Office of EMS and Trauma Systems, (206) 586-0310.

September 14-18—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 21-22—**Adult Critical Care.** Tacoma. Tues-Wed. Contact: Multicare, (206) 592-1221.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

September 24—**OB Issues.** Everett. Fri. Contact: PNMEI, (206) 258-6322.

September 24-26—**Rural Health Care Financing Conference.** Seattle. Fri-Sun. Contact: U/W School of Medicine, (206) 543-9952.

October 1-3—**Surgery Update.** Seattle. Thurs-Sat. Contact: U/W.

October 1-4—**Washington State Medical Association Annual Meeting.** Yakima. Thurs-Sun. Contact: WSMA.

October 8—**Family Practice Update.** Seattle. Fri. Contact: Providence Hospital, (206) 320-2552.

October 8-9—**Common Office Problems.** Tacoma. Fri-Sat. Contact: College of Medical Education, (206) 627-7137.

October 14—**Indoor Air Quality.** Seattle. Wed. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.

October 15-16—**Facial Surgery.** Seattle. Thurs-Fri. Contact: U/W.

October 15-17—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 22—**Pain Management.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

October 23—**NPCCare Consortium.** Seattle. Fri. Contact: Children's Hospital, (206) 526-2501.

October 30—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

October 30-31—**Black Culture Health.** Seattle. Fri-Sat. Contact: Providence Hospital, (206) 320-2552.

October 31-November 1—**PALS Instructor Course.** Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

November 6—**Infectious Disease Update.** Tacoma. Fri. Contact: PCMS CME.

November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.

November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

November 20—**GI Day.** Seattle. Fri. Contact: PCMS CME.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-11—**ACLS Course.** Tacoma. Thurs. Contact: PCMS CME.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

WYOMING

August 24-26—**Eighteenth Annual Tutorials in the Tetons.** Jackson Lake Lodge, Moran. 14.5 hrs. Contact: American College of Cardiology, (800) 257-4739. ◆

INSTRUCTIONS FOR AUTHORS

Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style*, 8th Edition).

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

Manuscripts should not exceed 3,000 words (15 double-spaced pages). Case Reports, Alerts, and Notices should not exceed 1,500 words. Lessons From the Practice should not exceed 1,000 words.

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include a nonstructured abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor **must be double-spaced** and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent galley proofs before publication.

All manuscripts will be subject to peer review to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous. Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal).

All accepted manuscripts are subject to copyediting, and the corresponding author is sent edited galley proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with his or her coauthors.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone number included.

The order of authorship is determined by the authors. All authors should meet the basic criteria for authorship (as stated below). Because order of authorship is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to add an explanation of the order of authorship in a footnote. In deciding on order, authors should be aware that many journals limit the number of authors listed in the table of contents and that the National Library of Medicine lists in MEDLINE only the first 10 authors.

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Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

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Acknowledgments

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, **must be double-spaced.**

The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

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Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and

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A form to order reprints will be sent to the author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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(Continued on Page 98)

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(Continued from Page 97)

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(Continued on Page 99)

(Continued from Page 98)

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(Continued on Page 100)

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The Western Journal of Medicine

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(Continued from Page 99)

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(Continued on Page 101)

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INTERNAL MEDICINE, FAMILY PRACTICE, URGENT CARE, OB/GYN, AND ACADEMICS

Positions in large metropolitan cities, urban, and rural communities with a concentration in the Great Lakes area and Plains States. Whether you prefer a cosmopolitan lifestyle, a city surrounded by nature and the beauty of four seasons, the peaceful rolling farm country, or perhaps life in historic villages—there is something for everyone. To discuss your practice preferences and these opportunities, please call our toll-free number, (800) 243-4353, or send your CV to STRELCHECK & ASSOCIATES, INC, 10624 N. Port Washington Rd, Mequon, WI 53092.

PEDIATRICIAN—SANTA MONICA. Associate needed for rapid takeover of busy, lucrative Pediatric practice. Good coverage weekends. Low overhead. Rare opportunity. Phone Lisa; (310) 829-1752 for details.

100 MEMBER multispecialty group seeks BC/BE Family Practitioners, Pediatricians, General Internists, Otolaryngologist, and Dermatologist in pleasant, growing northern California community two hours from San Francisco, Yosemite, and the Sierras. Excellent benefits, salary and facilities. Send CV to C. V. Allen, MD, Medical Director, 600 Coffee Rd, Modesto, CA 95355.

BC/BE FAMILY PHYSICIAN needed for large multispecialty group in San Jose, California. Includes Internal Medicine, Pediatrics, Gynecology, minor surgery with inpatient/outpatient responsibilities. Opportunities exist at main location and smaller facilities. Good call coverage exists. Competitive salary and benefits offered. Call Florence Korbus collect at (408) 999-7113 or send CV to MMS, 532 Race St, San Jose, CA 95126-3432.

SAN JOSE (SANTA CLARA COUNTY). Exceptional opportunity for a BC/BE Occupational Medicine Physician to become the medical director of an established Occupational Medicine program in a group practice. See patients and participate in management and growth of the program in an excellent market. Send CV to Number 267, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CENTRAL CALIFORNIA OCCUPATIONAL/FAMILY PRACTICE OPPORTUNITY. Growth oriented, dynamic group seeking BE/BC physician for Urgent Care/Occupational/Family Practice setting. Bilingual Spanish a real plus. Excellent salary, benefits, vacation, educational leave, paid malpractice. Please call (805) 322-2273, or send CV to Linda Brobst, Southwest Urgent Care, 5397 Truxtun Ave, Bakersfield, CA 93309.

INTERNIST OR FAMILY PHYSICIAN. Position available immediately. Nationally recognized comprehensive health care program for frail elderly residing in the northeast sector of San Francisco seeks Internist or Family Practice Physician for full-time employment. Work with a collegial, multidisciplinary team. Send CV to Darlene Yee, On Lok, Inc, 1441 Powell St, San Francisco, CA 94133. EOE.

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NEVADA—GASTROENTEROLOGIST. BC/BE needed to join General Intern practice in southern Nevada. Generous salary leading to full partnership. Interest in Internal Medicine preferred. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

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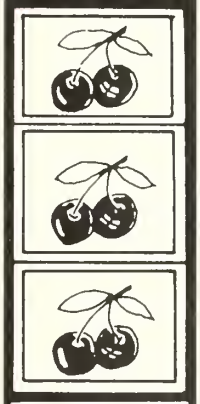

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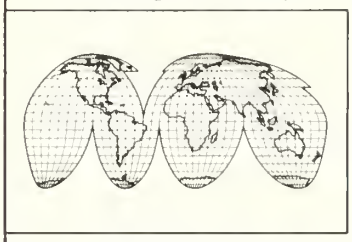

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ANCHORAGE, ALASKA. A 12 physician Internal Medicine group here is seeking their fourth Pulmonary specialist. Send CV to Gordon Crawford, Professional Relations, Humana Inc, Department WJ7-2L, PO Box 1438, Louisville, KY 40201-1438; or call toll free (800) 626-1590, ext #232.

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(Continued on Page 102)

(Continued from Page 101)

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SAN FRANCISCO BAY AREA. Two physician (with two physician assistants) General Practice/Family Practice group seeks BC/BE Family Practice, Internal Medicine, or Emergency Medicine practitioner capable of General Practice, to join thriving practice in rapidly growing Tri-Valley area 40 minutes east of San Francisco. No Obstetrics. Historic wine country; sophisticated professional and suburban patient base. Competitive salary first year, with bonus potential; consideration for partnership thereafter. Will also consider minimum one year employment contract not leading to partnership. Congenial atmosphere, attractive surroundings. Excellent financial opportunity in beautiful area. Send CV to James A. Blackwell, MD, Livermore Medical Clinic, 87 Fenton St, Ste 210, Livermore, CA 94550.

NATIONWIDE. Urgent Care, Family Practice, and Emergency Physicians are now needed in multiple locations which include Idaho, North Carolina, Virginia, Alabama, Arizona, and more. Please send your CV to Barbara Miller, Snake River Physicians, 2995 N Cole Rd, Ste 200B, Boise, ID 83704, or call Barbara Miller at (800) 688-5008.

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SOUTHERN CALIFORNIA. Family Practice physician position available in Riverside County. Guaranteed income, excellent benefits with early partnership. Send résumé to Number 265, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE—NEVADA, TEXAS, LOUISIANA, FLORIDA! Private practice opportunities available in Las Vegas and Reno, Nevada; Dallas, Victoria, and McAllen, Texas; New Orleans and Shreveport, Louisiana; West Palm Beach, Hollywood, and Plantation, Florida. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Ft Worth, TX 76185, or FAX (817) 927-0030.

PEDIATRICIANS—NEVADA, CALIFORNIA, TEXAS! Private practice opportunities available. Hospital sponsored with coverage or join an established group. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Ft Worth, TX 76185, or FAX (817) 927-0030.

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SEATTLE, WASHINGTON. FAMILY PHYSICIAN BC/BE, part- or full-time, wanted for a stimulating practice in a comprehensive Primary Care community clinic serving a diverse Asian/Pacific Islander population. OB required. Cantonese language skills helpful. Contact Debra Cavinta, Administrative Assistant, International District Community Health Center, 416 Maynard Ave S, Seattle, WA 98104; (206) 461-3617. EOE. Closing Date 9/30/92.

DISCOVER IDAHO. Urgent Care, Family Practice, and Emergency Physicians are now needed for a Low Acuity AFB Emergency Department, with an annual volume of 16K, and for an Urgent Care clinic with an annual volume of 15K. Here is your chance to live and work in one of America's fastest growing and most desirable areas. This attractive location offers the convenience and amenities of a major metropolitan area—where recreation is limited only by your imagination. Benefits include flexible scheduling, with the option of 12 or 24 hour shifts, competitive salaries, and no on-call duty. For more information please call or send your CV to Barbara Miller, Snake River Physicians, 2995 N Cole Rd, Ste 200B, Boise, ID 83704; (800) 688-5008.

GENERAL SURGEON—PHOENIX. A surgeon with one of the most established practices in Phoenix is seeking an associate to whom he will turn over the practice in several years. A surgeon in suburban Paradise Valley also needs an associate. For more information send CV to Gordon Crawford, Professional Recruitment, Humana Inc, Dept WJ7-2L, PO Box 1438, Louisville, KY 40201-1438, or call TOLL FREE (800) 626-1590, ext 257.

DON'T FORGET!

The deadline for submitting classifieds for the September issue of WJM is July 24. Send your advertisement to:

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(Continued on Page 103)

(Continued from Page 102)

BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

ACADEMIC PULMONOLOGIST/INTENSIVIST. Academic Pulmonary/Critical Care physician needed to join a three physician division of Respiratory and Critical Care Medicine at a 400-bed teaching hospital with Stanford University affiliation. The hospital has a full Internal Medicine residency training program and the division is part of a combined three hospital Pulmonary fellowship (SCVMC, Stanford University, and Palo Alto VA). The division's activities include supervision of medical students, residents and fellows, direction of a complete PFT LAB and an eight-bed MICU and participation in clinical research. Address inquiries to Carl M. Kirsch, MD, Division of Respiratory and Critical Care Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Ave, San Jose, CA 95128; or call (408) 299-5514. An equal opportunity and affirmative action employer.

DERMATOLOGIST. Immediate opportunity available for full- or part-time position with University affiliated multispecialty group in one of the most desirable cities. We offer a balanced lifestyle, competitive salary and an excellent benefit package. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

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CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled Family Practice physician to join our highly respected Urgent/Primary Care group with two beautiful Santa Cruz clinics. Flexible scheduling and a comprehensive benefit package. Rapid advancement to full partnership. Please send CV to Stuart Simon, MD, 6800 Soquel Dr, Aptos, CA 95003 and call (408) 662-3611.

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SOUTHERN CALIFORNIA. FAMILY PRACTICE, BC, energetic individual for a rapidly growing three physician practice. Will need to do clinic, hospital, and long term care facilities. Excellent compensation, rapid progression to partnership. Location is 10 minutes from the ocean in a fast growing area near Oceanside. Here is a chance to practice private medicine without bureaucratic problems. Call (619) 630-2422.

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UROLOGISTS—BC/BE needed for multispecialty group practice in central California and single-specialty group in Tucson, Arizona. Excellent compensation packages and partnership opportunity. All inquiries confidential. Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

CARDIOLOGIST, full-time BC/BE, invasive/noninvasive, inpatient/outpatient for practice at general hospital in association with two Cardiologists and five Internists leading to partnership. Excellent vacation schedule and competitive salary. Twenty-five minutes from San Francisco. Reply to San Mateo County Hospital, Attn: Mark Highman, MD, 222 W 39th Ave, San Mateo, CA 94403; (415) 573-3786.

(Continued on Page 104)

(Continued from Page 103)

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Alaska State Medical Association—4107 Laurel St, Anchorage 99508. (907) 562-2662. Annual Meeting: 1993, date and place to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1993, date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-13, 1992, Copper Mountain.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1992, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 30-August 1, 1992, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1992, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1993, date and place to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1993, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: October 1-4, 1992, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1993, date and place to be announced.

ADVERTISING INDEX

CIGNA HEALTHPLAN 100, 103

CLASSIFIED ADVERTISING 97, 98, 99, 100, 101, 102, 103, 104

ELI LILLY & COMPANY
Humulin 7

GLAXO INC.
Zantac . . . . . 3rd and 4th covers

IDAHO MEDICAL ASSOCIATION 17

JET PROPULSION LABS 99

JOURNAL WATCH 14

MARION MERRELL DOW
Cardizem 9, 10

MEAD JOHNSON PHARMACEUTICALS
Buspor 25, 26

PALISADES PHARMACEUTICALS INC.
Yocon 21

PHYSICIANS INTERINDEMNITY INSURANCE 15

RHÔNE-POULENC RORER
Dilocor 18, 19

G.D. SEARLE & COMPANY
Colon SR 3

SUTTER NEUROSCIENCE CENTER 91

UNIVERSITY SOUTHERN CALIFORNIA
University Hospital 5

UPJOHN COMPANY
Rogoine . . . . . 2nd cover, 1

US AIR FORCE 98

US ARMY 101

WELLS FARGO BANK 23

THE WESTERN JOURNAL OF MEDICINE
Cross-cultural Medicine II 89
Epitomes of Progress 1
Speciol Issues 16
Subscription 13

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Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg. Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:
General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/d.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks
Pregnancy: ***Teratogenic Effects; Pregnancy Category B***: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.
ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

reversible, but in exceedingly rare circumstances death has occurred.
Musculoskeletal: Rare reports of arthralgias
Hematologic: Blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia
Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.
OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.
DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling).
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternate dosage of 300 mg or 20 ml (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/d have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
GERD: The current recommended adult oral dosage is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.
HOW SUPPLIED: **Zantac® 300 Tablets** (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets

Store between 15° and 30° C (59° and 86° F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25° C (39° and 77° F). Dispense in light, light-resistant containers as defined in the USP/NF.

July 1990

Glaxo Pharmaceuticals
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The Western Journal of Medicine

VOLUME 157 • NUMBER 2 AUGUST 1992

BIOMEDICAL SCIENCE

133 Molecular Mimicry—Hypothesis or Reality?
N TSUCHIYA and R C WILLIAMS, Jr

ARTICLES

139 Physician-Patient Sexual Contact—Prevalence and Problems
N K GARTRELL, N MILLIKEN, W H GOODSON III, S THIEMANN, and B LO

144 *Mycobacterium avium* Complex and *Mycobacterium tuberculosis* in Patients Infected With the Human Immunodeficiency Virus
K M KERLIKOWSKE and M H KATZ

149 Quantitative Quality Assurance in a Community Hospital Pediatric Intensive Care Unit
B S FRANK and M M POLLACK

152 Screening Mammography Reports—Toward Clear, Concise Clinical Descriptions
W H HINDLE

CONFERENCES AND REVIEWS

154 Erythropoietin Therapy in Patients With Chronic Renal Failure
A J PINEVICH and J PETERSEN

158 The Second Century of the Antibody—Molecular Perspectives in Regulation, Pathophysiology, and Therapeutic Applications
Moderator: J BRAUN
Discussants: A SAXON, R WALL, and S L MORRISON

EPITOMES

Important Advances in Chest Diseases

ALERTS, NOTICES, AND CASE REPORTS

Long-standing Latent Idiopathic Hypoparathyroidism Discovered During Concurrent Central Nervous System Disease
B E WILSON and S TAWNEY

Cerebral Infarction as a Remote Complication of Childhood *Haemophilus influenzae* Meningitis
_ KERR and F M FILLOUX

Ehrlichiosis in a Visitor to Virginia
R W ARMSTRONG

Blood-Saturated Operating-Room Shoe Covers
R SUMMERS, M K BISWAS, S G PORTERA, and L MOORE

COMMENTARY

186 The 'R' Word—'Rationing' of Health Care and the Role of Academic Health Centers
R J BULGER

188 Physician Aid in Dying—What Physicians Say, What Patients Say
F J GIRSH

190 Editorial Comments: Assisted Suicide—What Euthanasia Activists Say, What People With Disabilities Say • The Popular Movement for Physician-Assisted Dying—What the Public Is Saying, What Physicians Are Hearing • Death, Politics, and Philosophy • Physician Aid in Dying—Finding the Middle Ground

EDITORIALS

195 Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia

CORRESPONDENCE

197 Acid-Base Disorders Revisited • Manifestations of Adult Varicella in the United States Navy, 1984-1987 • Successful Treatment of Markedly Symptomatic Patients With Type II Diabetes Mellitus Using High Doses of Sulfonylurea Agents

LESSONS FROM THE PRACTICE

201 Clinical Note—Doctor-Patient Bonding
R CRAWSHAW

202 Victor
H GOLDWATER

OTHER FEATURES

112 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington; Wyoming

125 In Memoriam

131 Subscription Information

153 Poem

203 Classified Advertising

212 Western State Medical Associations' Meetings

Detailed Table of Contents: 110, 118, 122

l Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State al Association, and the Wyoming Medical Society.

ed Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

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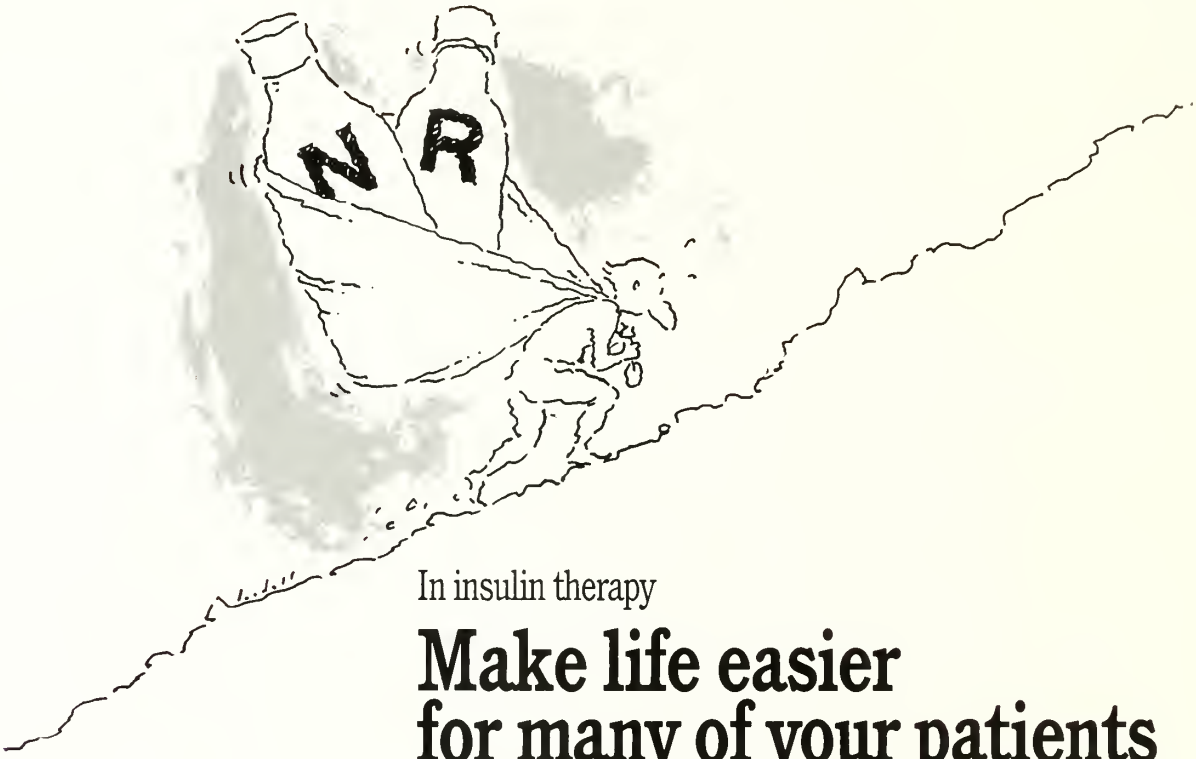

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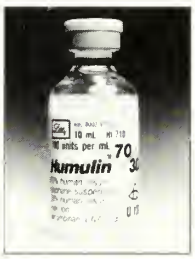

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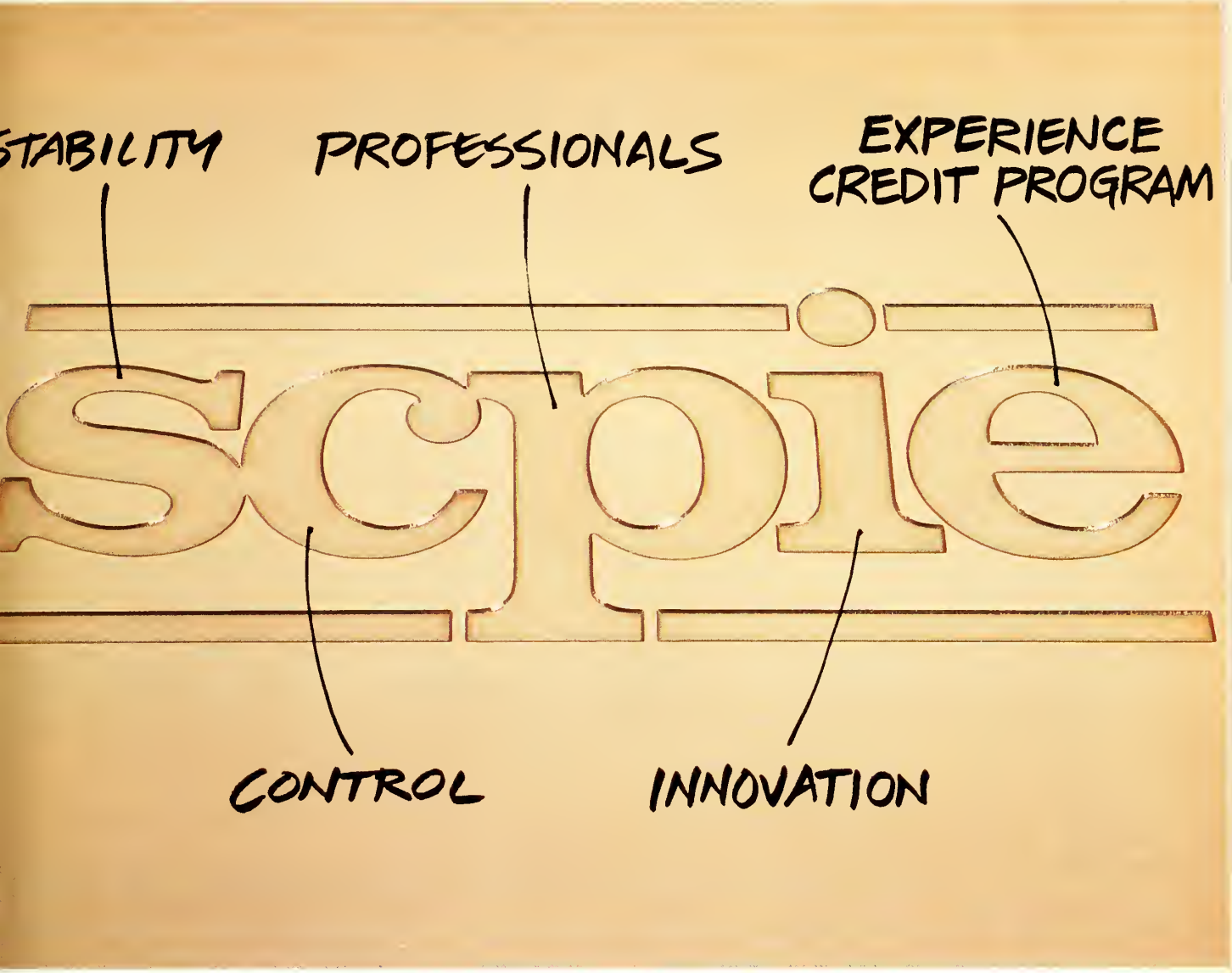

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Cully Cobb, M.D.

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The Western Journal of Medicine

VOLUME 157 • NUMBER 2 • AUGUST 1992

CONTENTS

BIOMEDICAL SCIENCE

133 **Molecular Mimicry—Hypothesis or Reality?**

NAOYUKI TSUCHIYA, MD, and RALPH C. WILLIAMS, Jr, MD

From the Department of Medicine and Physical Therapy, University of Tokyo School of Medicine, and the Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Florida College of Medicine, Gainesville.

ARTICLES

139 **Physician-Patient Sexual Contact—Prevalence and Problems**

NANETTE K. GARTRELL, MD; NANCY MILLIKEN, MD; WILLIAM H. GOODSON III, MD; SUE THIEMANN, MS; and BERNARD LO, MD

From the Departments of Psychiatry; Obstetrics, Gynecology, and Reproductive Sciences; Surgery; and Medicine and the Program in Medical Ethics, University of California, San Francisco.

144 ***Mycobacterium avium* Complex and *Mycobacterium tuberculosis* in Patients Infected With the Human Immunodeficiency Virus**

KARLA M. KERLIKOWSKE, MD, and MITCHELL H. KATZ, MD

From the General Internal Medicine Section, Department of Veterans Affairs Medical Center and the University of California, San Francisco, School of Medicine, and the Research Branch, AIDS Office, Department of Public Health, City and County of San Francisco.

149 **Quantitative Quality Assurance in a Community Hospital Pediatric Intensive Care Unit**

BARRY S. FRANK, MD, and MURRAY M. POLLACK, MD

From the Pediatric Intensive Care Unit, Washoe Medical Center, and the University of Nevada School of Medicine, Reno, and the Pediatric Intensive Care Unit, Children's National Medical Center, and the Departments of Pediatrics and Anesthesiology, George Washington University School of Medicine, Washington, DC.

152 **Screening Mammography Reports—Toward Clear, Concise Clinical Descriptions**

WILLIAM H. HINDLE, MD

From the Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles.

CONFERENCES AND REVIEWS

154 **Erythropoietin Therapy in Patients With Chronic Renal Failure**

ANTHONY J. PINEVICH, MD, and JEFFREY PETERSEN, MD, MRCP

From the Division of Nephrology, Mercy Hospital, Pittsburgh, Pennsylvania, and the Division of Nephrology, Stanford University School of Medicine, Stanford, California.

158 **The Second Century of the Antibody—Molecular Perspectives in Regulation, Pathophysiology, and Therapeutic Applications**

Moderator: JONATHAN BRAUN, MD, PhD
Discussants: ANDREW SAXON, MD; RANDOLPH WALL, PhD; and SHERIE L. MORRISON, PhD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine, University of California, Los Angeles, School of Medicine. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Chest Diseases

Items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

169 **Occupational Asthma**

JOHN R. BALMES, MD

(Continued on Page 118)

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†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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ALLERGY/IMMUNOLOGY

September 19—**Asthma Care for the Allergist of the Nineties.** Los Angeles Society of Allergy and Clinical Immunology at Westin South Coast Plaza Hotel, Costa Mesa. Sat. 8 hrs. Contact: Diann Smith, PO Box 84443, Los Angeles 90073. (310) 450-6092.

ANESTHESIOLOGY

October 22-25—**American Pain Society: 11th Annual Meeting.** American Pain Society at San Diego. Thurs-Sun. Contact: APS, 5700 Old Orchard Rd, Skokie, IL 60077-1057. (708) 966-5595.

November 6-8—**Anesthesiology Update: 1992.** UCD at Monterey Plaza Hotel. Fri-Sun. 14 hrs. $350. Contact: UCD.

November 20-21—**Pain Management Conference.** UCD at Silverado Country Club. Fri-Sat. Contact: UCD.

January 6-9—**Anesthesia Update.** UCSD at Hotel del Coronado. Wed-Sat. Contact: UCSD.

January 29-31—**31st Clinical Conference in Pediatric Anesthesiology.** Children's Hospitals Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

September 12—**Stress Echocardiography.** Sutter Health at Hyatt Regency, Sacramento. Sat. Contact: Sutter Health, (916) 733-3883.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Medical Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

September 25-26—**Coronary Interventions: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sat. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 1-3—**Cardiology Update—1992.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12 hrs. $445. Contact: ACC, (800) 257-4739.

January 21-23—**Cardiology '93.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, Conference Manager, PO Box 2586, La Jolla 92038. (619) 459-1564.

DERMATOLOGY

October 17-18—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

January 15-17—**Practical Dermatology & Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Wed-Fri. Contact: UCSD.

EMERGENCY MEDICINE

August 17-21—**Emergency Medicine Symposia II.** UCSD at Basic Science Building. Mon-Fri. Contact: UCSD.

August 19-23—**Wilderness Medicine: 1992.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Gene Allred, MD, PO Box 321, Yreka 96097. (800) 888-5632.

October 2-3—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Marina Del Rey. Fri-Sat. 15 hrs. Contact: Kathy Hester, (800) 451-7475.

October 10—**Emergency Medicine.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

October 19-23—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 26-30—**21st Annual Topics in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 32 hrs. $560. Contact: UCSF.

October 28-November 1—**Wound Management Workshop.** UCSD at San Diego Hilton Beach & Tennis Resort. Wed-Sun. Contact: UCSD.

October 29-November 1—**14th Year Biannual Wound Management Workshop.** UCSD at La Jolla Marriott. Thurs-Sun. 18 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 5-6—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Thurs-Fri. 15 hrs. $295-$495. Contact: Kathy Hester, (800) 451-7475.

November 9-13—**Emergency Medicine Symposia III.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

December 6-11—**Current Concepts in Emergency Care: 13th Annual Conference.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Jeannine Whidbee, 4192 Meridian Ave, Bellingham, WA 98226. (800) 544-9269.

December 7-11—**Emergency Medicine Symposia II.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

January 13-17—**The California Trauma Conference.** UCSD at Hotel del Coronado. Mon-Fri. 20 hrs. $400. Contact: UCSD.

January 18-22—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

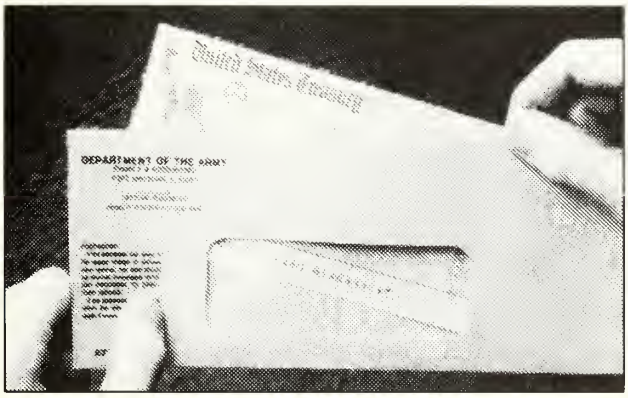
UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 116)

ANESTHESIOLOGISTS AND SURGEONS: COULD YOU USE AN EXTRA $12,500?



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ABSTRACTS AUGUST 1992

(Tsuchiya N, Williams RC Jr: Molecular mimicry—Hypothesis or reality? West J Med 1992 Aug; 157:133-138)

A number of observations support molecular mimicry as a possible pathogenetic mechanism in diseases such as acute rheumatic fever, reactive arthritis after enteric infection or associated with Reiter's syndrome, myasthenia gravis, or even in rheumatoid arthritis. Molecular mimicry can be defined as a sharing of epitopes in linear or 3-dimensional presentation on disparate proteins from entirely different sources—for instance, group A streptococcal membranes and human cardiac myosin. How exposure to or infection with organisms sharing molecular similarity with antigens of the human host can evade tolerance and actually induce a self-reacting humoral or cellular immune response is still not clear; however, a large body of evidence has now been accumulated that documents apparent molecular mimicry mechanisms in these disorders. In some diseases, the molecular mimicry appears to involve human target organs and specific components of the infectious organism, whereas in others the host HLA cell surface molecules appear to share antigens with presumed bacterial or viral initiators of disease.

MOLECULAR MIMICRY
AUTOIMMUNE DISEASE
ACUTE RHEUMATIC FEVER
REACTIVE ARTHRITIS
SYSTEMIC LUPUS ERYTHEMATOSUS
ANKYLOSING SPONDYLITIS
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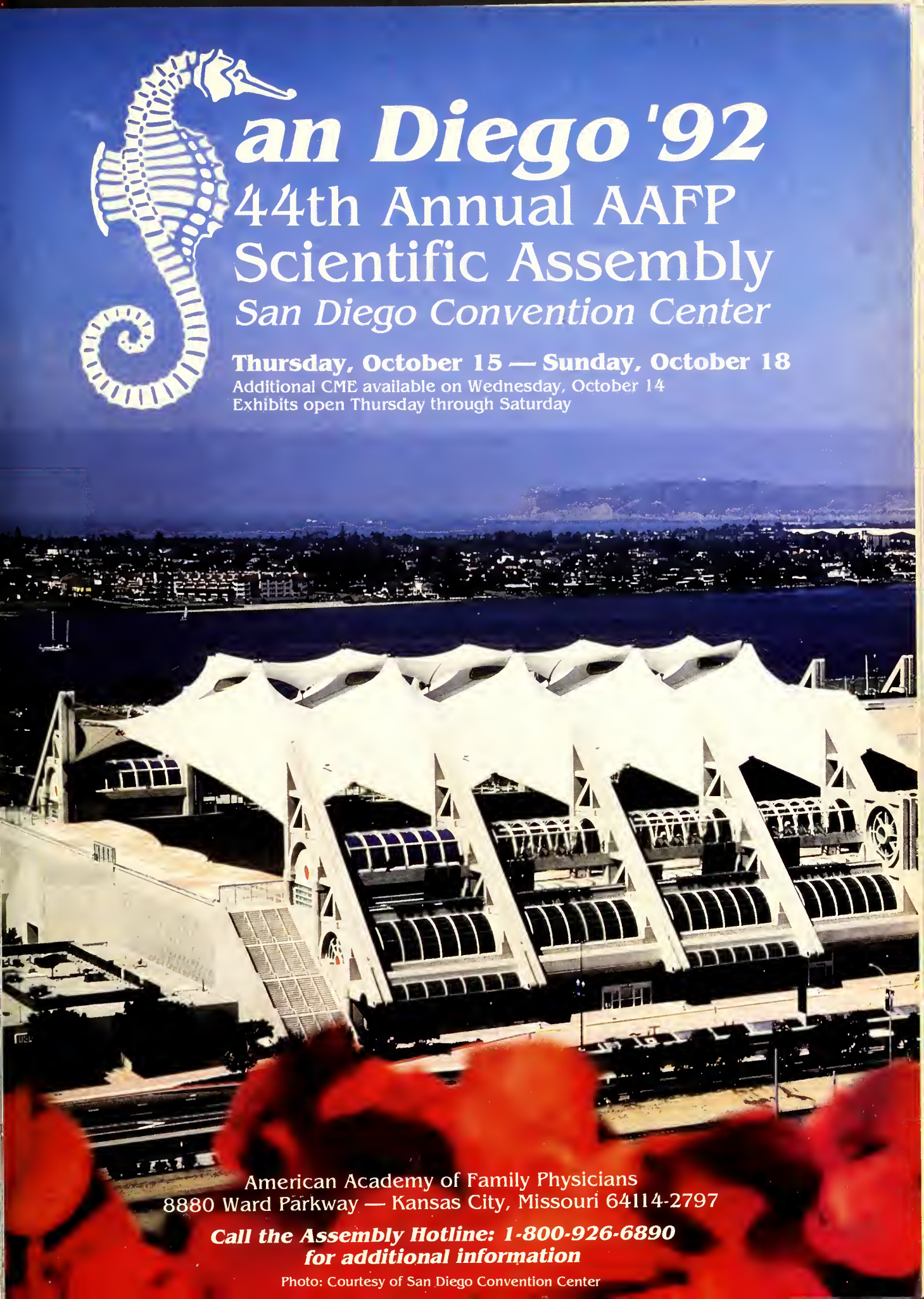
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(Continued from Page 112)

January 23-30—**Wound Management.** UCSD at Royal Waikoloan, Kohala Coast, Island of Hawaii. 1 week. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

FAMILY PRACTICE/PRIMARY CARE

August 21-23—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 21-23—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Loews Coronado Bay Resort, Coronado Island, San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

September 23-25—**7th Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $485. Contact: UCSF.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

October 15-18—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Maui Inter-Continental Hotel, Hawaii. Thurs-Sun. 16 hrs. $281-$375. Contact: UCLA Extension.

November 12-15—**CME/GOLF Meeting.** Nevada Academy of Family Physicians at Rio Hotel, Las Vegas. Thurs-Sun. 17 hrs. $225. Contact: Shone Ariotti, 895 Adams Blvd, Boulder City, NV 89005. (702) 293-0406.

GERIATRICS

September 26—**Selected Topics in Geriatric Medicine.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sat. 6 hrs. $40. Contact: UCLA Extension.

November 16-18—**Geriatrics Update—1992.** Sharp Memorial Hospital at Loew's Coronado Bay Resort. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASES

September 19—**AIDS.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, (916) 733-3883.

November 13-15—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

December 14-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

INTERNAL MEDICINE

August 23-28—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. 25 hrs. $480. Contact: UCD.

August 29-September 3—**10th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Sat-Thurs. 51 hrs. $850. Contact: UCLA Extension.

September 11-17—**Progress and Review in Internal Medicine & Board Review Course.** UCSD at Sheraton Grande Torrey Pines, San Diego. Sun-Thurs. 41 hrs. $500-$650. Contact: UCSD.

September 17-19—**American Gastroenterological Association 1992 Fall Postgraduate Course.** AGA at Westin St. Francis, San Francisco. Thurs-Sat. Contact: SLACK Inc, 6900 Grove Rd, Thorofare, NJ 08086-9447. (609) 848-1000.

November 5-7—**Otolaryngology Update: 1992.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $395. Contact: UCSF.

November 10-14—**VIIth International Symposium on the Biology of Vascular Cells.** Scripps Clinic and Research Foundation at Princess Resort Mission Bay, San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

NEUROLOGY

October 9-11—**Neurology for the Non-Neurologist.** Medical Education Resources at Parc Fifty-Five, San Francisco. Fri-Sun. Contact: MER, 1500 W Canal, Ste 500, Littleton, CO 80120-4528. (303) 798-5731.

October 23-24—**Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery and Anesthesiology.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. Contact: UCLA Division of Neurosurgery, (310) 206-0626.

OB/GYN

October 3-4—**Ultrasound Update: 1992.** UCD at Sacramento. Sat-Sun. Contact: UCD.

October 24—**Women's Health and Breast Cancer.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. Contact: UCD.

December 3-5—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas. Thurs-Sat. $250. Contact: Brenda Ram, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

OCCUPATIONAL/ENVIRONMENTAL

October 19-30—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. 1½ wks. 80 hrs. $1,400. Contact: UCSF.

November 2-6—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

January 25-February 5—**Occupational & Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. 1½ weeks. 80 hrs. $1400. Contact: UCSF.

ONCOLOGY

October 12-18—**18th Annual Lukes Lymphoma Conference.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Sun. 25 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

October 24—**Melanoma and Pigmented Lesions.** Stanford University Medical Center at Fairchild Auditorium, Stanford. Sat. Contact: STAN.

October 26-28—**16th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, Cancer Symposium, 5665 Oberlin Dr, # 110, San Diego 92121. (619) 453-6222.

November 5-8—**Prostate Cancer.** Sutter Health at Hyatt Regency, Sacramento. Thurs-Sun. Contact: Sutter Health, (916) 733-3883.

OPHTHALMOLOGY

October 10—**The Diabetic Eye.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. $50. Contact: UCD.

December 10-11—**Glaucoma Management.** UCSF at Ritz-Carlton, San Francisco. Thurs-Fri. Contact: UCSF.

ORTHOPEDICS

October 31—**Orthopedics Symposium.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

November 5-6—**Low Back Pain and Its Relation to the Sacroiliac Joint.** UCSD at San Diego Convention Center. Thurs-Fri. 12 hrs. $335. Contact: UCSD.

November 19-21—**San Diego Spine Symposium.** UCSD at San Diego Marriott. Thurs-Sat. Contact: UCSD.

December 3—**9th Annual Symposium on Common Musculoskeletal Problems: Current Concepts in Diagnosis and Management of Arthritis.** VA Medical Center Sepulveda. Thurs. 6 hrs. Contact: Arun Mehta, MD, VA Med Ctr, RMS 117, Sepulveda 91343-2036. (818) 895-9344.

December 9-13—**Fall Symposium on Back Pain.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

PATHOLOGY

October 10—**Fine Needle Aspiration: Advanced Tutorial XXI.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

October 17—**32nd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Irvine Marriott. Sat. Contact: Sylvie Tarro, (310) 641-8152.

October 26-30—**Urological Pathology: Current Concepts and Recent Developments.** American Society of Clinical Pathologists at Santa Barbara. Mon-Fri. 25.5 hrs. $690. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (312) 738-1336.

(Continued on Page 119)

AMERICAN MEDICAL WOMEN'S ASSOCIATION

77TH ANNUAL MEETING

NOVEMBER 11-15, 1992

WESTIN ST. FRANCIS HOTEL

AMERICAN MEDICAL WOMEN'S ASSOCIATION

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Join Us in San Francisco to Learn About
The Latest on a Wide Range of Issues Including:

WOMEN'S HEALTH

- Breast Disease
- AIDS in Women and Children
- Coronary Heart Disease in Women
- Reproductive Health
- Violence Against Women
- Health Care for the Homeless

WOMEN IN MEDICINE

- Gender Equity
- Maternity and Medicine
- Balancing Personal and Professional Roles

GUEST SPEAKERS

Vivian Pinn, MD, Director, Office of Research on Women's Health, NIH

Frances Conley, MD, Professor of Surgery, Stanford University School of Medicine

Nancy Snyderman, MD, Medical Correspondent, ABC Television's *Good Morning America*

Dianne Feinstein, Candidate, U.S. Senate (Invited)

The American Medical Women's Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. CME Workshops: Up to 23 hours depending on choices.

Pre-register by October 1, 1992 for discounted rates.
- On-site registration available
- Daily rates available

For further information and complete program contact:

AMERICAN MEDICAL WOMEN'S ASSOCIATION AT 703-838-0500

(Continued from Page 110)

169 **Antibiotics for Pneumonia**
MICHAEL S. BERNSTEIN, MD

170 **Diagnosis of Pulmonary Embolism**
ANTHONY M. COSENTINO, MD

171 **Thrombolytic Treatment of Pulmonary Embolism**
HAROLD I. PALEVSKY, MD, and THOMAS A. RAFFIN, MD

171 **Lung-Assist Devices**
DAVID M. GELMONT, MD

172 **Bronchiolitis Obliterans Organizing Pneumonia**
OM P. SHARMA, MD

173 **Advances in Pulmonary Biopsy Techniques**
NORMAN W. RIZK, MD

173 **Lung Transplantation**
E. CLINTON LAWRENCE, MD; JAMES THEODORE, MD; and VAUGHN A. STARNES, MD

174 **Monoclonal Therapy for Bacteremia and Sepsis**
JOE GUGLIELMO, PharmD, and JEANINE P. WIENER-KRONISH, MD

174 **Conventional Treatment of Cystic Fibrosis**
BERTRAND J. SHAPIRO, MD

175 **Aerosolized Bronchodilators**
ARCHIE F. WILSON, MD, PhD

175 **Screening for Obstructive Sleep Apnea Using Pulse Oximetry**
ADRIAN J. WILLIAMS, MD, and MYRON STEIN, MD

ALERTS, NOTICES, AND CASE REPORTS

177 **Long-standing Latent Idiopathic Hypoparathyroidism Discovered During Concurrent Central Nervous System Disease**
BRUCE E. WILSON, MD, and SURESH TAWNEY, MD
From the Department of Internal Medicine, University of Nevada School of Medicine, Las Vegas.

179 **Cerebral Infarction as a Remote Complication of Childhood *Haemophilus influenzae* Meningitis**
LYNNE KERR, MD, PhD, and FRANCIS M. FILLOUX, MD
From the Departments of Neurology and Pediatrics and Psychiatry, University of Utah School of Medicine, Salt Lake City.

182 **Ehrlichiosis in a Visitor to Virginia**
ROBERT W. ARMSTRONG, MD
From the Department of Medicine, Community Hospital and Rehabilitation Center, Los Gatos, California.

184 **Blood-Saturated Operating-Room Shoe Covers**
PAUL R. SUMMERS, MD; MANOJ K. BISWAS, MD; S. G. PORTERA; and LINDA MOORE, PhD
From the Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, and the Department of Obstetrics and Gynecology, Tulane University School of Medicine, New Orleans, Louisiana.

COMMENTARY

186 **The 'R' Word—'Rationing' of Health Care and the Role of Academic Health Centers**
ROGER J. BULGER, MD
From the Association of Academic Health Centers, Washington, DC.

188 **Physician Aid in Dying—What Physicians Say, What Patients Say**
FAYE J. GIRSH, EdD
Dr Girsh is a clinical and forensic psychologist in private practice in San Diego, California.

190 **Assisted Suicide—What Euthanasia Activists Say, What People With Disabilities Say**
PAUL K. LONGMORE, PhD
Dr Longmore is Visiting Assistant Professor, Department of History, Stanford University, Stanford, California.

(Continued on Page 122)

CONTINUING MEDICAL EDUCATION

(Continued from Page 116)

PEDIATRICS

August 24-26—**Pediatrics Update: 1992.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

September 21-26 & October 19-24—**Lactation Management Education Program.** UCSD at Wellstart, San Diego. Mon-Sat. Contact: UCSD.

October 19-22—**17th Annual Pediatrics for the Practitioner.** Long Beach Memorial at Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact: Eunice Larson, MD, (310) 595-3422.

PSYCHIATRY

November 13-15—**38th Annual Group Therapy Symposium.** UCSF at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. Contact: UCSF.

PULMONARY MEDICINE

September 17-19—**11th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $410. Contact: UCSF.

RADIOLOGY

September 9-11—**8th Annual Sonography Update.** UCSD at Hotel del Coronado, San Diego. Wed-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 11-13—**UCSD Ultrasound and Cardiovascular Technology Registry Review Conference.** UCSD at Towne & Country Hotel, San Diego. Fri-Sun. 23.5 hrs. $350-$400. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 12-13—**Sonography Registry Review.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 20-23—**UCLA Digital Radiography and Image Management Networking Conference.** UCLA Medical Center at Miramar Sheraton Hotel, Santa Monica. Sun-Wed. 16 hrs. $345. Contact: UCLA.

September 21-23—**Digital Radiography and Image Management Networking.** UCLA Radiological Sciences at Miramar Sheraton Hotel, Santa Monica. Mon-Wed. 16 hrs. $345. Contact: UCLA Radiological Sciences, (310) 206-7435.

October 1-4—**Western Neuroradiological Society Annual Meeting.** Western Neuroradiological Society at Ritz-Carlton, San Francisco. Thurs-Sun. 11.5 hrs. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 24-25—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-30—**17th Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25.25 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 29-November 1—**Current Concepts of Magnetic Resonance.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 19.5 hrs. $450-$550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 30-November 1—**12th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 2-6—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Mon-Fri. 15 hrs. $400. Contact: UCSD.

November 13-15—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 28-January 2—**Year End Review of Imaging and Intervention.** UCSD at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Sat. 25 hrs. $550-$595. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 16-17—**Interventional Radiology Update.** Stanford University at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 7.5 hrs. $200-$250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 18-20—**Neuroradiology Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 17.5 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 120)

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(Continued from Page 119)

January 21-24—**Breast Imaging Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 17.25 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

September 14-18—**What's New in Vascular Surgery: A Comprehensive Review and Update.** UCLA at Miramar Sheraton, Santa Monica. Mon-Fri. 34 hrs. $469-$625. Contact: UCLA Extension.

October 16-18—**Hip and Knee Reconstructive Surgery: 1992.** UCLA at Westin Hills Resort, Rancho Mirage. Fri-Sun. 14 hrs. $595. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. Sun-Sat. 36 hrs. $500-$995. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. 1 week. Contact: UCLA Extension.

GENERAL/MULTIDISCIPLINARY

September 24-27—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. Thurs-Sun. Contact: UCLA Extension.

December 24-29—**Advances in Medicine '92.** Hawaii Medical Association at Kaanapali Beach, Maui, Hawaii. Fri-Wed. 16 hrs. $450. Contact: Joe Harrison, MD, PO Box 833, Makawao, HI 96768. (808) 878-7657.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

August 17-21—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

August 21-22—**Second Annual Musculoskeletal Infection Society Meeting.** University of Colorado's CME in the Rockies at Snowmass Village, Snowmass. Fri-Sat. Contact: U of Colo.

September 10-13—**Colorado Medical Society Annual Meeting.** Copper Mountain. Contact: CMS, PO Box 17550, Denver 80217-0550.

September 10-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

September 18-23—**Primary Care Computing.** University of Colorado's CME in the Rockies at the Given Institute, Aspen. Fri-Wed. Contact: U of Colo.

September 25-26—**Montrose Memorial Hospital Fall Clinics.** Montrose Pavilion, Montrose. Fri-Sat. Contact: N. Robert Brethouwer, DO, (303) 249-2211.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 9-13—**38th Annual Family Practice Review.** University of Colorado Health Sciences Center, Denver. Wed-Sun. Contact: U of Colo.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

January 22-24—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs Medical Center at Beaver Run Resort and Conference Center, Breckenridge. Fri-Sun. Contact: Victoria Hall or Karen Babcock, (303) 393-2826, or FAX (303) 393-4656.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

August 15—**Transfusion Medicine: Oxygen Transport and Hemostasis.** Holiday Inn Pyramid, Albuquerque. Sat. Contact: UNM SOM.

September 7-11—**Mammography Update.** Eldorado Hotel, Santa Fe. Mon-Fri. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

September 8-9—**Critical Care Obstetrics.** Holiday Inn Pyramid, Albuquerque. Tues-Wed. Contact: UNM SOM.

September 10-12—**Perinatal Care Update.** Holiday Inn Pyramid, Albuquerque. Thurs-Sat. Contact: UNM SOM.

September 11-12—**Essentials of Health Care for the Elderly.** UNM Conference Center, Albuquerque. Fri-Sat. Contact: UNM SOM.

September 18-19—**New Mexico Chapter, American College of Surgeons, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Fri-Sat. Contact: William Abbott, MD, 711 Encino Pl NE, Albuquerque 87102. (505) 843-7901; or Bonnie Smith at the New Mexico Medical Society, (505) 828-0237 or (800) 748-1596.

September 26-27—**Pediatric Infectious Diseases for the '90s.** Plaza Hotel, Las Vegas. Sat-Sun. Contact: Marilyn Stark, New Mexico Chapter, American Academy of Pediatrics, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431; or George Bunch, MD, 501 7th St, Las Vegas 87701. (505) 425-3566.

October 8-11—**The American Academy of Pain Management 1992 Annual Conference.** Hyatt Regency Hotel, Albuquerque. Thurs-Sun. Contact: Janice Mohr, American Academy of Pain Management, 3600 Sisk Rd, Ste 2-D, Modesto, CA 95356. (209) 545-0754.

October 9-10—**Effective Psychotherapy: Research and Practice.** Sheraton Old Town Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

October 22-24—**Practical Orthopaedics in the Primary Care Setting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 22-24—**Infectious Disease: Issues and Challenges in Obstetrics and Gynecology.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 30-November 1—**The Emotional Life of the Infant: Clinical Applications.** Hilton Hotel, Albuquerque. Fri-Sun. Contact: UNM SOM.

November 6-7—**Update for Radiographers.** Four Seasons Quality Inn, Albuquerque. Fri-Sat. Contact: UNM SOM.

December 3-5—**American College of Physicians, New Mexico Chapter, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

December 11-12—**Trauma Update 1992.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

(Continued on Page 126)

SEMINARS IN OBSTETRICS AND GYNECOLOGY

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"OFFICE GYNECOLOGY"
September 19-20, 1992

Saturday, September 19, 1992
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Treatment of Symptomatic Vulvar Lesions"** – Dr. Leo Twiggs
- 8:30–9:30 **"Management of the Menopausal Woman"** – Dr. William Spellacy
- 9:30–10:30 **"Treating the Abnormal Pap Smear"** – Dr. Twiggs
- 10:30–11:30 **"Hyperprolactemia and Galactorrhea"** – Dr. Spellacy
- 11:30–12:30 **"New and Future Methods of HPV Therapy"** – Dr. Twiggs

Sunday, September 20, 1992
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Treatment of Symptomatic Vulvar Lesions"** – Dr. Leo Twiggs
- 8:30–9:30 **"Management of the Menopausal Woman"** – Dr. William Spellacy
- 9:30–10:30 **"Treating the Abnormal Pap Smear"** – Dr. Twiggs
- 10:30–11:30 **"Hyperprolactemia and Galactorrhea"** – Dr. Spellacy
- 11:30–12:30 **"New and Future Methods of HPV Therapy"** – Dr. Twiggs

"PERINATAL MEDICINE"
November 14–15, 1992

Saturday, November 14, 1992
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Preconception Counseling"** – Dr. Robert Resnik
- 8:30–9:30 **"Heart Disease in Pregnancy"** – Dr. Stephen Clark
- 9:30–10:30 **"Fetal Assessment"** – Dr. Jeffrey Lipshitz
- 10:30–11:30 **"Antepartum Fetal Surveillance of the Postdated Pregnancy"** – Dr. Jeffrey Phelan
- 11:30–12:30 **"The Role of Lupus Anticoagulant and Anticardiolipin Antibodies in Reproductive Loss"** – Dr. Resnik

Sunday, November 15, 1992
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Terbutaline Pump Therapy"** – Dr. Phelan
- 8:30–9:30 **"Managing Complications of Severe Pregnancy Induced Hypertension"** – Dr. Clark
- 9:30–10:30 **"The Evaluation and Management of the Patient with Intrauterine Growth Retardation"** – Dr. Resnik
- 10:30–11:30 **"Role of Amnioinfusion"** – Dr. Phelan
- 11:30–12:30 **"Management of the Post-Partum Hemorrhage"** – Dr. Clark

"REPRODUCTIVE ENDOCRINOLOGY"
February 6-7, 1993

Saturday, February 6, 1993
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"The Future of GYN"** – Dr. Alan DeCherney
- 8:30–9:30 **"Pathophysiology of Adhesion Formation and Treatment at Pelviscopy"** – Dr. Michael Diamond
- 9:30–10:30 **"RU - 486"** – Dr. DeCherney
- 10:30–11:30 **"Intrauterine Insemination"** – Dr. Andrew Friedman
- 11:30–12:30 **"Endocrine Aspects of Menopause"** - Dr. DeCherney

Sunday, February 7, 1993
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Modern Diagnosis of Ectopic Pregnancy"** – Dr. Bruce Shapiro
- 8:30–9:30 **"Surgical Treatment of Ectopic Pregnancy"** – Dr. Diamond
- 9:30–10:30 **"Distal Tubal Disease; IVF vs. Surgery"** – Dr. Friedman
- 10:30–11:30 **"GNRH Use in Management of Uterine Myomata and Endometriosis"** – Dr. Friedman
- 11:30–12:30 **"Hysteroscopic Treatment of Intrauterine Lesions"** – Dr. Diamond

"CONTROVERSIES IN OBSTETRICAL MANAGEMENT"
July 17-18, 1993

Saturday, July 17, 1993
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Fetal Assessment: Which Test is Best?"** – Dr. Jeffrey Lipshitz
- 8:30–9:30 **"Timing and Mechanisms of Perinatal Neurological Injury"** – Dr. Barry S. Schifrin
- 9:30–10:30 **"Twins"** – Dr. Thomas J. Benedetti
- 10:30–11:30 **"Cervical Cerclage vs. Preterm Labor"** – Dr. Julian T. Parer
- 11:30–12:30 **"Dysfunctional Labor"** – Dr. Schifrin

Sunday, July 18, 1993
- 7:00 a.m. **Registration & Breakfast**
- 7:30–8:30 **"Intrapartum Fetal Monitoring"** – Dr. Parer
- 8:30–9:30 **"Ketoacidosis"** – Dr. Benedetti
- 9:30–10:30 **"Pre-Eclampsia Including HELLP Syndrome"** – Dr. Parer
- 10:30–11:30 **"Invasive Hemodynamic Monitoring"** – Dr. Benedetti
- 11:30–12:30 **"Will the C/Section Rate Ever Exceed 100%?"** - Dr. Schifrin

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(Continued from Page 118)

191 **The Popular Movement for Physician-Assisted Dying—What the Public Is Saying, What Physicians Are Hearing**
CHRISTINE K. CASSEL, MD
Dr Cassel is Chief, Section of General Internal Medicine, Division of Biological Sciences, University of Chicago, Pritzker School of Medicine, Chicago, Illinois.

192 **Death, Politics, and Philosophy**
ALBERT R. JONSEN, MD
Dr Jonsen is Professor and Chair, Department of Medical History and Ethics, University of Washington School of Medicine, Seattle.

193 **Physician Aid in Dying—Finding the Middle Ground**
FAITH FITZGERALD, MD
Dr Fitzgerald is Vice Chair and Program Director, Department of Internal Medicine, University of California, Davis, School of Medicine, Sacramento.

EDITORIALS

195 **Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia**
ALLAN J. ERSLEV, MD
Dr Erslev is with the Department of Medicine, Cardezo Foundation for Hematologic Research, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania.

CORRESPONDENCE

197 **Acid-Base Disorders Revisited**
ROBERT I. CARSON and JOSEPH I. SHAPIRO, MD
RICHARD J. HABER, MD, Responds

197 **Manifestations of Adult Varicella in the United States Navy, 1984-1987**
LCDR NATHAN H. MULL, MC, USNR; CPT DENNIS E. AMUNDSON, MC, USN; LCDR WARING R. TRIBLE, MC, USN; LCDR TIMOTHY B. CALL, MC, USN

199 **Successful Treatment of Markedly Symptomatic Patients With Type II Diabetes Mellitus Using High Doses of Sulfonylurea Agents**
MAYER B. DAVIDSON, MD

LESSONS FROM THE PRACTICE

201 **Clinical Note—Doctor-Patient Bonding**
RALPH CRAWSHAW, MD

202 **Victor**
HARLAND GOLDWATER, MD
Dr Goldwater is on sabbatical from a private general practice.

OTHER FEATURES

112 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington; Wyoming**
125 **In Memoriam**
131 **Subscription Information**
153 **Poem**
203 **Classified Advertising**
212 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%
Dizziness	22 (7%)	6 (2.8%
Edema	19 (6%)	2 (0.9%
Bradycardia	19 (6%)	3 (1.4%
ECG Abnormality	13 (4.1%)	3 (1.4%
Asthenia	10 (3.2%)	1 (0.5%
Constipation	5 (1.6%)	2 (0.9%
Dyspepsia	4 (1.3%)	1 (0.5%
Nausea	4 (1.3%)	2 (0.9%
Palpitations	4 (1.3%)	2 (0.9%
Polyuria	4 (1.3%)	2 (0.9%
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%
Hypotension	3 (1%)	1 (0.5%
Insomnia	3 (1%)	1 (0.5%
Rash	3 (1%)	1 (0.5%
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions repo placebo-controlled trials in patients receiving CARDIZEM CD up to 360 rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARD Capsules involving over 3000 patients, the most common events (ie, than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than

Cardiovascular: Angina, arrhythmia, AV block (second- or third-d bundle branch block, congestive heart failure, ECG abnorm hypotension, palpitations, syncope, tachycardia, ven extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abno hallucinations, insomnia, nervousness, paresthesia, personality somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeu elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irr hyperglycemia, hyperuricemia, impotence, muscle cramp congestion, nocturia, osteoarticular pain, polyuria, sexual diffic

The following postmarketing events have been reported infrequ patients receiving CARDIZEM: alopecia, erythema multiforme, ex dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic increased bleeding time, leukopenia, purpura, retinopat thrombocytopenia. In addition, events such as myocardial infarcti been observed which are not readily distinguishable from the nature of the disease in these patients. A number of well-documented generalized rash, characterized as leukocytoclastic vasculitis, hav reported. However, a definitive cause and effect relationship betwe events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages c

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages o

CARDIZEM® CD Product Information as of October 1991

CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Ma Prevey ML, et al. *JAMA* 1989;261(22):3273-3274

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In Memoriam

California Medical Association

ABRAHAM, SAMUEL V., Encino. Died Feb 20, 1992, aged 93. Graduate of University of Illinois, Chicago, 1928. Licensed in California in 1931. Dr Abraham was a member of the Los Angeles County Medical Association.

❧

ANDERSON, GERALD J., San Diego. Died May 1992, aged 60. Graduate of University of Minnesota Medical School, Minneapolis, 1959. Licensed in California in 1963. Dr Anderson was a member of the San Diego County Medical Society.

❧

BLINN, JOHN F., JR, Stockton. Died Jun 21, 1992, aged 73. Graduate of Washington University School of Medicine, St Louis, Missouri, 1943. Licensed in California in 1944. Dr Blinn was a member of the San Joaquin County Medical Society.

❧

CANNON, THOMAS P., East San Diego. Died May 1992, aged 67. Graduate of University of Minnesota Medical School, Minneapolis, 1951. Licensed in California in 1953. Dr Cannon was a member of the San Diego County Medical Society.

❧

GERLACH, KARL D., Huntington Beach. Died Apr 1992, aged 56. Graduate of University of Miami School of Medicine, Miami, Florida, 1964. Licensed in California in 1968. Dr Gerlach was a member of the Orange County Medical Association.

❧

GRIFFIN, RONALD A., Loma Linda. Died Apr 1992, aged 59. Graduate of University of California, San Francisco, 1957. Dr Griffin was a member of the San Bernardino County Medical Society.

❧

KAVENEY, ROBERT E., San Diego. Died Jun 8, 1992, aged 59. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1959. Licensed in California in 1964. Dr Kaveney was a member of the San Diego County Medical Society.

❧

LUSIGNAN, HARRY, Monterey. Died May 7, 1992, aged 88. Graduate of Stanford University, Stanford, California, 1929. Dr Lusignan was a member of the Monterey County Medical Society.

❧

PONT, MAYNARD E., Castro Valley. Died Mar 26, 1992, aged 60. Graduate of University of Michigan, Ann Arbor, 1955. Licensed in California in 1958. Dr Pont was a member of the Alameda-Contra Costa Medical Association.

❧

ROBB, ROBERT C., South Laguna. Died Mar 29, 1992, aged 99. Graduate of State University of New York College of Medicine, Syracuse, 1935. Licensed in California in 1947. Dr Robb was a member of the Orange County Medical Association.

ROSENBERG, JOEL M., Berkeley. Died Jun 1992, aged 48. Graduate of University of California, Los Angeles, 1969. Dr Rosenberg was a member of the Alameda-Contra Costa Medical Association.

❧

SCHMUTZ, MELVIN A., Vallejo. Died Jun 9, 1992, aged 76. Graduate of Temple University School of Medicine, Philadelphia, 1941. Licensed in California in 1941. Dr Schmutz was a member of the Solano County Medical Society.

❧

STEELE, ASHBY, Felton. Died May 1, 1992, aged 90. Graduate of University of Arkansas School of Medicine, Little Rock, 1929. Licensed in California in 1937. Dr Steele was a member of the Santa Cruz County Medical Society.

❧

TURNER, JOSEPH E., Monterey. Died May 1992, aged 70. Graduate of University of Kansas, Kansas City, 1952. Licensed in California in 1954. Dr Turner was a member of the Monterey County Medical Society.

❧

WATSON, FRANCES R., Burlingame. Died Apr 4, 1992, aged 85. Graduate of Stanford University, Stanford, California, 1934. Licensed in California in 1935. Dr Watson was a member of the San Mateo County Medical Society.

New Mexico Medical Society

FARRIS, LEE L., Albuquerque. Died May 29, 1992, aged 71. Graduate of University of Tennessee, Memphis, 1954. Licensed in New Mexico in 1958. Dr Farris was a member of the Greater Albuquerque Medical Association.

❧

HUDSON, HEBER SCOTT, Albuquerque. Died Mar 22, 1992, aged 68. Graduate of University of Minnesota, 1950. Licensed in New Mexico in 1968. Dr Hudson was a member of the Greater Albuquerque Medical Association.

❧

SERVICE, ALLEN C., Capitan. Died Jan 1992, aged 85. Graduate of University of Pennsylvania, Philadelphia, 1934. Dr Service was a member of the Chaves County Medical Society.

❧

SLEEPER, DONALD C., Ocate. Died Apr 3, 1992, aged 60. Graduate of University of Kansas School of Medicine, Kansas City, 1958. Licensed in New Mexico in 1979. Dr Sleeper was a member of the Rio Arriba County Medical Society.

❧

WALDMAN, MILTON, Albuquerque. Died Mar 31, 1992, aged 80. Graduate of Lausanne University, 1941. Licensed in New Mexico in 1975. Dr Waldman was a member of the Greater Albuquerque Medical Association.

(Continued from Page 120)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 10—**Monthly Meeting** (Sponsor: UOS). Thursday evening. Contact: UOS.

September 16-19—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CS: Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

UV: Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 21-22—**Regional CME Network Meeting.** Seaside, Oregon. Fri-Sat.

August 28-29—**Pediatric Orthopedics.** Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

August 28-30—**17th Annual Washington State EMS Conference.** Spokane. Fri-Sun. Contact: Office of EMS and Trauma Systems, (206) 586-0310.

September 14-18—**Family Practice Review.** Seattle. Mon-Fri. Contact: U/W.

September 21-22—**Adult Critical Care.** Tacoma. Tues-Wed. Contact: Multicare, (206) 592-1221.

September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.

September 24—**OB Issues.** Everett. Fri. Contact: PNMEI, (206) 258-6322.

September 24-26—**Rural Health Care Financing Conference.** Seattle. Fri-Sun. Contact: U/W School of Medicine, (206) 543-9952.

October 1-3—**Surgery Update.** Seattle. Thurs-Sat. Contact: U/W.

October 1-4—**Washington State Medical Association Annual Meeting.** Yakima. Thurs-Sun. Contact: WSMA.

October 8—**Family Practice Update.** Seattle. Fri. Contact: Providence Hospital, (206) 320-2552.

October 8-9—**Common Office Problems.** Tacoma. Fri-Sat. Contact: College of Medical Education, (206) 627-7137.

October 14—**Indoor Air Quality.** Seattle. Wed. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.

October 15-16—**Facial Surgery.** Seattle. Thurs-Fri. Contact: U/W.

October 15-17—**Endoscopic Sinus Surgery.** Seattle. Thurs-Sat. Contact: U/W.

October 22—**Pain Management.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

October 23—**NPCCare Consortium.** Seattle. Fri. Contact: Children's Hospital, (206) 526-2501.

October 30—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

October 30-31—**Black Culture Health.** Seattle. Fri-Sat. Contact: Providence Hospital, (206) 320-2552.

October 31-November 1—**PALS Instructor Course.** Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

November 6—**Infectious Disease Update.** Tacoma. Fri. Contact: PCMS CME.

November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.

November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

November 20—**GI Day.** Seattle. Fri. Contact: PCMS CME.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-11—**ACLS Course.** Tacoma. Thurs. Contact: PCMS CME.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

August 24-26—**Eighteenth Annual Tutorials in the Tetons.** Jackson Lake Lodge, Moran. 14.5 hrs. Contact: American College of Cardiology, (800) 257-4739. ◆

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FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

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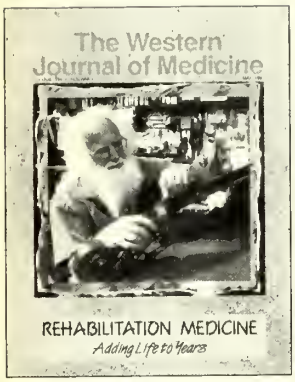

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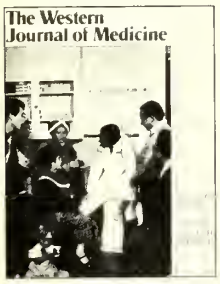

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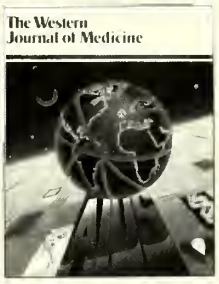

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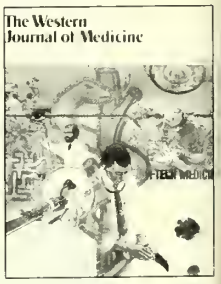

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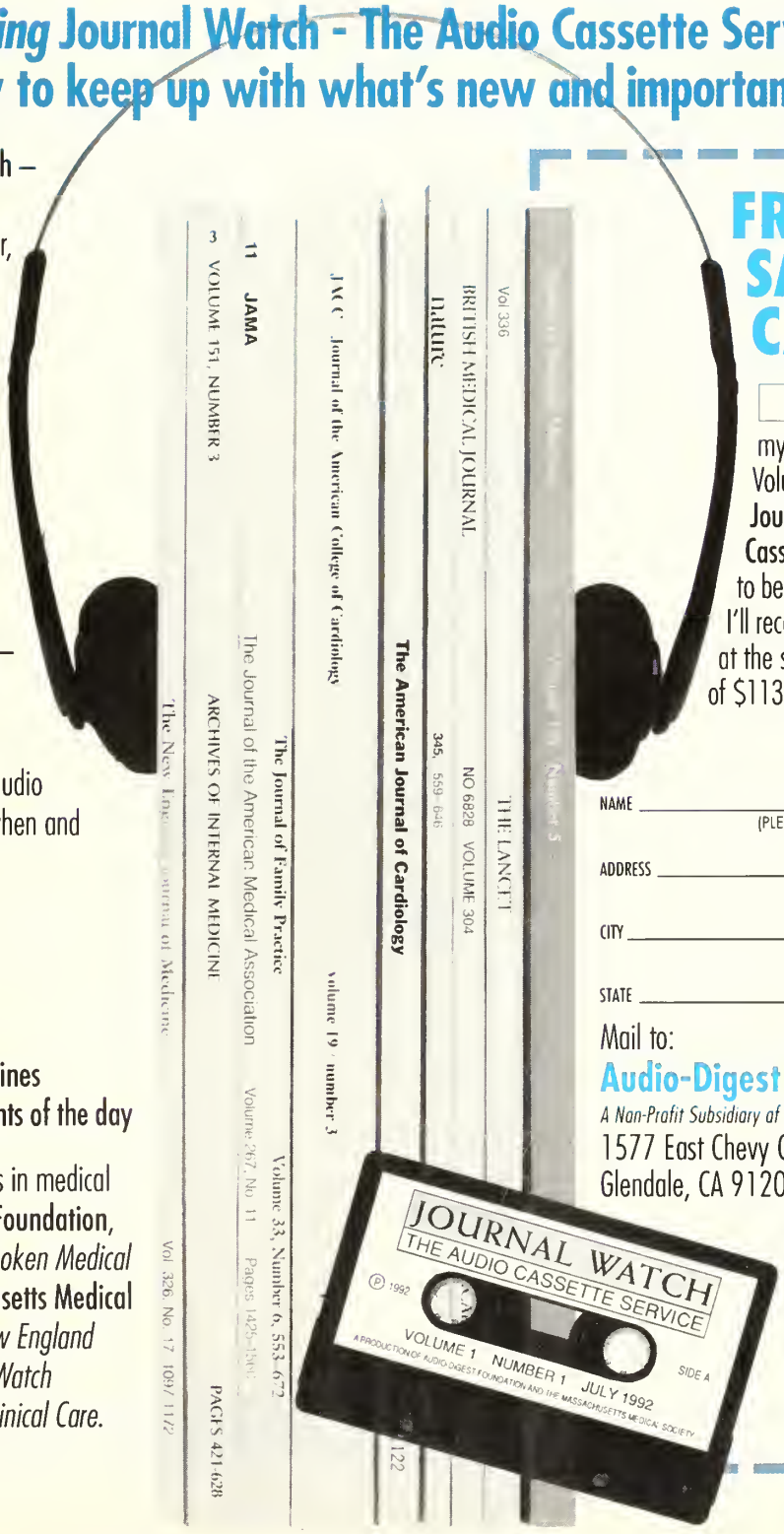

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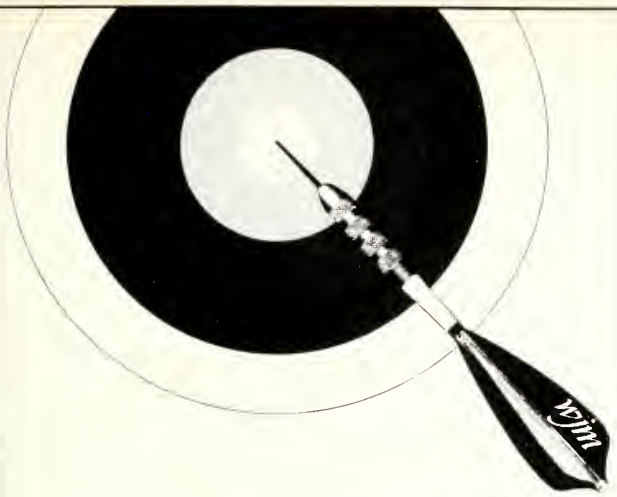

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1. Data from randomized, controlled studies. On file, SmithKline Beecham Pharmaceuticals.

2. Palmer RH, Frank WO, Rockhold FW, et al. Cimetidine 800 mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. *J Clin Gastroenterol.* 1990;12(suppl 2):S29-S34

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Biomedical Science

Molecular Mimicry—Hypothesis or Reality?

NAOYUKI TSUCHIYA, MD, *Tokyo, Japan; and* RALPH C. WILLIAMS, Jr, MD, *Gainesville, Florida*

Presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 5-6, 1992.

A number of observations support molecular mimicry as a possible pathogenetic mechanism in diseases such as acute rheumatic fever, reactive arthritis after enteric infection or associated with Reiter's syndrome, myasthenia gravis, or even in rheumatoid arthritis. Molecular mimicry can be defined as a sharing of epitopes in linear or 3-dimensional presentation on disparate proteins from entirely different sources—for instance, group A streptococcal membranes and human cardiac myosin. How exposure to or infection with organisms sharing molecular similarity with antigens of the human host can evade tolerance and actually induce a self-reacting humoral or cellular immune response is still not clear; however, a large body of evidence has now been accumulated that documents apparent molecular mimicry mechanisms in these disorders. In some diseases, the molecular mimicry appears to involve human target organs and specific components of the infectious organism, whereas in others the host HLA cell surface molecules appear to share antigens with presumed bacterial or viral initiators of disease.

(Tsuchiya N, Williams RC Jr: Molecular mimicry—Hypothesis or reality? West J Med 1992 Aug; 157:133-138)

Burnet's original hypothesis that forbidden clones resurrected themselves periodically to initiate an autoimmune response represented one of the first attempts to explain the occurrence of autoimmune disease.[1] Although initially attractive as a rational way of explaining the vexing enigma of autoimmune mechanisms, the clonal selection theory with its implied episodic emergence of forbidden clones has not held up well against much subsequent empiric data. Other possible mechanisms whereby the self becomes its own target are now being considered and actively pursued to attempt to explain the occurrence of autoimmune phenomena and the actual genesis of diseases such as systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, reactive arthritis, and myasthenia gravis. In this analysis we review the clinical and laboratory observations that have prompted the concept of molecular mimicry as an underlying mechanism that could initiate an autoimmune reaction. Moreover, we will also attempt to examine strong supporting evidence and other aspects that may constitute important reservations for accepting molecular mimicry as the major avenue for inducing autoimmune phenomena.

Acute Rheumatic Fever

Clearly the most compelling example of molecular mimicry can be found in the case of acute rheumatic fever. A number of clinical observations and laboratory phenomena appear to support an underlying mechanism of molecular mimicry as being a major initiator of the acute symptoms and subsequent chronic manifestations of the disease. Previously thought to be uncommon and dying out in the United States and Canada, rheumatic fever has re-emerged as a major health problem, with sizable epidemics occurring recently in Utah[2] and several portions of the Midwest, Tennessee, and Pennsylvania.[3-6]

Virtually all of the clinical manifestations of acute rheumatic fever, including chorea, acute migratory polyarthritis, and acute carditis and valvulitis, can be explained on the basis of molecular mimicry mechanisms. This is related to the astonishing number of epitopes that appear to be shared between various human tissues and components of β-hemolytic group A streptococci. Perhaps no single group of bacteria has been as exhaustively studied for molecular mimicry as β-hemolytic group A streptococci. After the initial recognition of cross-reactivity between group A streptococcal components and human myocardium by Kaplan and co-workers.[7-9] the immunochemical basis for this cross-reactivity was extensively refined by Zabriskie and Freimer[10] and later by Van de Rijn and associates.[11] Through direct immunologic observations, human valvular glycoproteins were found to cross-react with components of group A streptococci.[12,13] Moreover, group A streptococcal antigens have also been shown to cross-react with components of the human cardiac conduction system.[14] Long after the initial rheumatic episode, levels of streptococcal group A carbohydrate antibodies were found to be markedly elevated in serum from patients with rheumatic heart disease and previous acute rheumatic fever.[15] Moreover, when such patients later underwent cardiac valve resection and artificial valve replacement, levels of anti-group A carbohydrate antibody often declined precipitously.[16] These observations appeared to indicate that an immune response to autologous tissues had been induced based on the previous repeated, intense antigenic exposures in early childhood to group A streptococcal carbohydrate during clinical or possibly subclinical rheumatic fever episodes. Thus, the removal of the diseased cardiac valves at an operative procedure such as mitral valve resection and the insertion of an artificial heart valve were followed by a rapid decline in levels of anti-group A-specific anticarbohydrate

From the Department of Medicine and Physical Therapy, University of Tokyo School of Medicine, Tokyo (Dr Tsuchiya), and the Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Florida College of Medicine, Gainesville (Dr Williams).

Supported in part by National Institutes of Health grants AM13824 and AR40438.

Reprint requests to Ralph C. Williams, Jr, MD, Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Florida College of Medicine, Box 100221, Gainesville, FL 32610.

ABBREVIATIONS USED IN TEXT

HSV = herpes simplex virus
Ig = immunoglobulin

antibody. The presence of large quantities of group A-cross-reactive glycoprotein in the patients' diseased heart valves apparently stimulated an antigenic response sufficient to maintain high levels of group A carbohydrate-specific antibody within the circulation. Thus, in some way the long-standing hyperreactivity of such patients to group A carbohydrate epitopes was being enhanced and continued through cardiac valvular autoantigen reinforcement.

On many occasions, we and others, using immunofluorescence or immunoperoxidase and highly specific polyclonal or monoclonal antibodies to various streptococcal components,[17] have examined heart valves surgically removed because of chronic rheumatic heart disease for residual traces of streptococcal antigens. In all cases, no direct evidence for the retention of streptococcal antigens within macrophages or other phagocytes was obtained. The failure to find streptococcal antigenic material in such phagocytes years after the last acute episode of rheumatic fever does not rule out continued low levels of messenger RNA capable of providing the original antigenic message induced by the group A streptococcal epitopes in question. Precisely how such fundamental questions relating to the mechanisms driving autoimmune processes in the body can be approached experimentally remains to be determined.

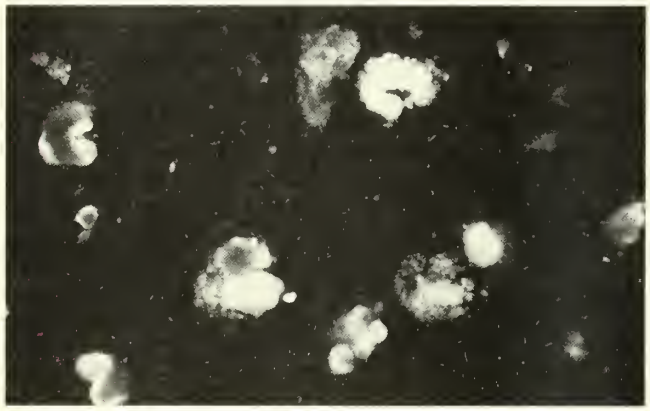

Figure 1.—Antineuronal antibody from the serum of a child with acute rheumatic fever stains neuronal cytoplasm in a frozen section of normal human brain through the caudate nucleus. Bright cytoplasmic immunofluorescence is seen in a number of positively staining neurons (original magnification × 350).

For years acute or subacute chorea has been accepted as a major manifestation of acute rheumatic fever. Indeed, when Bland examined a large number of patients who had had chorea years previously as the major manifestation of a rheumatic episode, roughly a quarter showed clinical evidence for rheumatic valvular lesions—predominantly mitral insufficiency or mitral stenosis.[18] The connection between the brain and the heart became clearer when it was found that many patients with acute rheumatic fever and such choreiform episodes show immunoglobulin (Ig) G antibodies in their serum that cross-react with neuronal cytoplasmic antigens of nerve cells situated in the various anatomic locations of the brain. These nerve cells—subthalamic and caudate nucleus neurons—are probably involved in the generation of choreiform movements.[19] An example of this remarkable molecular mimicry is shown in Figure 1. The antineuronal antibodies present in the serum of children with Sydenham's chorea can be completely absorbed using purified preparations of group A streptococcal membranes.

The arthritis that is often characteristic of an acute attack of rheumatic fever has been called migratory because it often will affect a number of joints in succession. Never does the migratory arthritis of acute rheumatic fever affect a single joint for more than a few days or a week. This transient and evanescent quality distinguishes the joint manifestations of acute rheumatic fever from other conditions affecting children, such as juvenile rheumatoid arthritis, systemic lupus erythematosus, or septic arthritis. Recently the joint manifestations of acute rheumatic fever have also been ascribed to molecular mimicry.[20] Direct cross-reactivity has been demonstrated between components of streptococcal M protein and joint structures such as cartilage glycoproteins and other components of synovial tissues. Cross-reactive antibodies that were capable of complement activation were demonstrated in these patients' serum with arthritis as a clinical manifestation of their acute rheumatic fever syndrome. Previous studies of rheumatic fever synovial fluids had documented complement component profiles consistent with activation of the complement cascade.[21] It thus appeared that the acute arthritis associated with rheumatic fever could be due to antistreptococcal antibodies directly cross-reacting with joint glycoprotein components and activating the complement cascade to induce an intense local inflammatory reaction in the joints.

Thus the carditis, valvular lesions, chorea, and arthritis of acute rheumatic fever have now all been shown to involve cross-reacting epitopes between the components of group A β-hemolytic streptococci and human cardiac and joint tissue, and the central nervous system. Moreover, some evidence for cell-mediated immune responsiveness in the case of rheumatic carditis and particulate streptococcal products has also been presented.[22-24] A partial catalogue of the extent of the remarkable molecular mimicry that has now been documented between the group A streptococcus and various sites and tissues involved in acute rheumatic fever is presented in Table 1.

Ankylosing Spondylitis and Reactive Arthritis

Molecular mimicry has also been implicated in the genesis of ankylosing spondylitis and the spondyloarthropathy associated with reactive arthritis.[28-31] A number of previous observations appeared to support molecular mimicry. Thus levels of anti-*Klebsiella pneumoniae* antibodies were reported to be higher in patients with ankylosing spondylitis than in controls.[32] Direct cross-reactions were reported between polyclonal and monoclonal antibodies to various products and the HLA-B27.5 gene product.[30,31] This latter seemed important because more than 95% of patients with ankylosing spondylitis and 70% to 80% of patients with reactive arthritis such as Reiter's syndrome were positive for HLA-B27. Schwimmbeck and co-workers analyzed the protein sequence data base and found a remarkable six amino acid homology (QTDRED) between the HLA-B27.5 sequence and that of the *K pneumoniae* nitrogenase reductase (Table 2).[33] It was estimated at the time that the chances of this exact sequence homology occurring were less than 1 in 20 million! They found elevated levels of antibodies to peptides containing the homologous QTDRED sequence in

TABLE 1.—*Molecular Mimicry Between Epitopes Within the Group A β-Hemolytic* Streptococcus *and Human Tissues Involved in the Acute Inflammatory Disorder of Acute Rheumatic Fever*

Group A Streptococcal Component	*Human Cross-Reacting Tissue Elements*	*Reference Source*
Membranes	Myocardial sarcolemmal membrane	Zabriskie and Freimer, 1966[10]; Van de Rijn et al, 1977[11]
Cell walls	Myocardial cells	Kaplan, 1963[7]
Glycoproteins	Heart valve glycoproteins	Goldstein et al, 1967[12]
Membranes	Caudate and subthalamic nuclei neuronal cytoplasm	Husby et al, 1976[19]
Antigens	Cardiac conduction system	Kasp-Grouchowska and Kingston, 1977[14]
Protein	Cardiac sarcolemmal membrane	Dale and Beachey, 1985[25]; Kraus et al, 1990[26]
Carbohydrate	Cardiac valvular structures	Dudding and Ayoub, 1968[15]
Membranes	Cardiac myosin	Krisher and Cunningham, 1985[27]
M protein	Articular cartilage and synovium	Baird et al, 1991[20]

HLA-B27-positive patients with ankylosing spondylitis and in HLA-B27-positive patients with Reiter's syndrome and reactive arthritis.[33]

Implied with these findings was a direct mechanism of molecular mimicry between autologous HLA-B27.5 antigenic epitopes and those present on *K pneumoniae* nitrogenase. When Husby and associates used rat antiserum to several HLA-B27.5 peptides in conjunction with similar antiserum to *K pneumoniae* nitrogenase peptides to actually stain synovial tissues of patients with ankylosing spondylitis or reactive arthritis, strong cross-reactivity was repeatedly demonstrated.[34] Thus, the part of the class I HLA-B27.5 antigens encompassing the homologous QTDRED sequence was strongly expressed on both synovial membrane lining cells and vascular endothelium of vessels in inflamed synovium of patients with ankylosing spondylitis. Similar staining patterns of synovial lining cells and vascular endothelium were also found using rat antiserum to homologous *K pneumoniae* peptides, confirming the impression of direct molecular mimicry at the actual tissue level. Subsequent attempts, however, to confirm the presence of humoral antibody to both *K pneumoniae* peptides and HLA-B27 peptides were only clearly positive for antibody to HLA-B27.5 peptides.[35,36] No notably elevated levels of humoral antibody to *K pneumoniae* peptides were found in the large ankylosing spondylitis or reactive arthritis-Reiter's disease populations examined. Moreover, the *K pneumoniae* peptide did not seem to cross-react with patients' anti-B27 peptide antibodies.

Subsequently, a plasmid called pHS-2, derived from the arthritogenic strains of *Shigella flexneri*, was also found to encode a sequence containing a homologous stretch of amino acids (Table 2).[37] We found that affinity-purified anti-B27.5 peptide antibodies significantly cross-reacted with the peptide derived from pHS-2.[36] Using peptides containing point substitution of amino acids, it was clearly shown that leucine common in HLA-B27.5 and pHS-2 but not in *K pneumoniae* nitrogenase was critical for the cross-reactivity. Surprisingly, another homologous sequence was found in *Yersinia enterocolitica*, also associated with reactive arthritis (Table 2).[38] Substantially higher proportions of patients with ankylosing spondylitis showed elevated levels of antibody against the homologous sequence, although the cross-reactivity with the HLA-B27.5 sequence was not clearly observed.[38] Such common occurrence of homologous sequences among Enterobacteriaceae might confer uniqueness to HLA-B27, which could possibly be associated with autoimmunity or an inability to clear microorganisms because of cross-tolerance. Thus, direct mechanisms of molecular mimicry may contribute to the understanding of the underlying pathogenic mechanisms that may be occurring in reactive arthritis or the spondyloarthropathies.

An experimental approach to the puzzle of precisely how the presence of class I HLA-B27.5 may predispose persons to the development of ankylosing spondylitis or reactive arthritis was reported by Hammer and colleagues in 1990.[39] These workers produced Lewis rats transgenic for HLA-B27.5 plus

TABLE 2.—*Sequence Homology Between Proteins of Possible Relevance to Autoimmune Disease*

Protein	*Amino Acid Sequence*
HLA-B27.5	A Q T D R E D L R T L
Klebsiella pneumoniae nitrogenase	R Q T D R E D E L I I
pHS-2	A Q T D R H S L S C I
YOP1	S K T D R E N S V S I
Acetylcholine receptor α chain	P E S D Q P D L
Herpes simplex virus type 1 gD	P N A T Q P E L
Mycobacterial hsp65	T F G L Q L E L T
Proteoglycan link protein	T A V V A L E L Q
Epstein-Barr virus gp110	E Q N Q E Q K R A A Q R A A
HLA-DR4, Dw4	K D L L E Q K R A A V D T Y

β_2-microglobulin and found that such animals spontaneously developed a disease similar in many respects to ankylosing spondylitis. Moreover, the disease seemed to develop in direct proportion to the actual transgene dose effect—that is, transgenic animals with multiple copies of the HLA-B27 transgene seemed much more likely to have the disease than did transgenic rats with low numbers of transgenes expressed. Our own studies of serum specimens from these same transgenic animals (provided by J. D. Taurog, MD) indicated that a low proportion (15%) of the rats studied also produced humoral antibody to the HLA-B27.5 peptide AKAQTDREDLRTLLRY and CAQTDRHSLSY, a peptide representing the potential cross-reacting epitope in the pHS-2 plasmid. The levels and distribution of the anti-B27 or anti-pHS-2 peptide antibodies, however, did not correlate directly

with the presence of the experimental disease in the rats (unpublished data, May 1992). This observation appeared to represent a strong caveat against accepting direct molecular mimicry as a major factor in at least the experimental model of ankylosing spondylitis and reactive arthritis in transgenic Lewis rats. Whether a process of molecular mimicry occurs as a basic driving event in the spondyloarthritides still remains to be determined.

An important additional reservation as to how molecular mimicry might be involved in diseases such as ankylosing spondylitis or reactive arthritis is that some element of cell-mediated immunoreactivity against shared class I HLA-B27 and bacterial antigens would be expected. We, however, were unable to demonstrate T-cell hyperreactivity against peptides such as those representing a class I B27.5 epitope reacting with autologous patients' IgG antibody when a large number of both B27-positive and B27-negative patients with ankylosing spondylitis were examined using a sensitive migration inhibition factor assay.[35] Thus, although high levels of antibody reacting with the B27.5 peptide could be demonstrated, no evidence for T cell-mediated immune reactivity could be found in the same patients. Much still needs to be learned concerning T cell-mediated immune reactivity and presumed autoimmune reactions that may be involved in disorders such as ankylosing spondylitis or Reiter's syndrome.

Myasthenia Gravis

Myasthenia gravis has been classified for some time as an autoimmune disease. Even before anti-acetylcholine receptor antibodies were perceived to be part of the pathogenetic mechanisms of the disease, patients with myasthenia were being treated by total thymectomy on the rather marginal evidence that T cells and T-cell control might play a fundamental role in fostering the disease.[40,41] When the immunogenicity of the acetylcholine receptor began to be recognized and the various structural and antigenic components of the receptor identified, a large body of experimental evidence began to accumulate that indicated that a combined humoral and cellular immune response to immunodominant epitopes of the acetylcholine receptor appeared to be the major mechanism of pathogenesis of the myasthenia gravis disease process.[42-44] No clear insight into how vital neuromuscular transmitters such as acetylcholine receptors actually become autoantigenic has yet emerged. A natural alternative or explanation that could fit with the clinical and experimental evidence might be that an exogenous stimulus was introduced or became available in affected persons in whom myasthenia then develops on the basis of a profound immune reaction that they mount against antigenic epitopes of the acetylcholine receptor. The key question here is, what actually initiates the immune reactivity against self-acetylcholine receptors? Again, Schwimmbeck and co-workers have produced a body of experimental observations that support a possible molecular mimicry mechanism in myasthenia gravis.[45] Data-bank searches have elicited evidence that certain exposed or hydrophilic residues of herpes simplex virus type 1 (HSV-1) contain homologies with sequences in the acetylcholine receptor (Table 2).[45] Patients with myasthenia show humoral antibodies that react with linear peptide sequences present in HSV-1 glycoprotein D.[45] During the course of this work, no evidence was forthcoming concerning cell-mediated or T-cell immune responses to the linear HSV-1 epitopes in patients with myasthenia.

This work on presumed molecular mimicry and an etiopathologic initiating event in myasthenia gravis provides the essence of the problem discussed here. From a clinical standpoint, there is little evidence that would support the notion that the disease is induced by HSV-1 infection. Moreover, various epidemiologic studies suggest that 60% to 90% of the population in developed western countries—the United States, Canada, Europe—have had an original HSV-1 infection at some time during their childhood or early adulthood. Clearly many persons who have had a primary or even secondary HSV-1 infection must be at risk of having antibodies to HSV-1 that could then cross-react with the acetylcholine receptor and eventually result in myasthenia gravis. The wide prevalence of HSV-1 infection and the rarity of myasthenia gravis are difficult to reconcile when the facts available are considered.

Rheumatoid Arthritis

Three lines of evidence suggest the possible involvement of molecular mimicry mechanisms in several aspects of rheumatoid arthritis.

Mycobacterial 65-Kilodalton (kd) Heat Shock Protein (hsp65)

Initial information concerning the relevance of mycobacterial antigen came from an adjuvant arthritis model. Arthritis resembling human rheumatoid arthritis or Reiter's disease could be induced by a single injection of complete Freund's adjuvant, a mixture of mycobacterial antigen and mineral oil. Holoshitz and associates isolated a $CD4^+$ T-cell clone, A2b, that was capable of inducing adjuvant arthritis when transferred to another susceptible rat strain.[46] Of interest, A2b was shown to proliferate, recognizing not only mycobacterial antigen but also cartilage proteoglycan, strongly suggesting a molecular mimicry mechanism in adjuvant arthritis.

The epitope for A2b was subsequently mapped as the peptide (180 to 188) of the mycobacterial 65-kd heat shock protein using deletion mutants of the recombinant protein.[47] The possibility of mimicry between hsp65 and proteoglycan seemed to be strengthened when partial amino acid sequence homology was found between this epitope and a proteoglycan link protein (Table 2).[48] Subsequent studies using the overlapping peptides, however, clearly showed that A2b was fully stimulated by the peptide TFGLQLE (180 to 186), and each single substitution of amino acid by alanine virtually abolished the reactivity.[49] Thus, the possibility of the direct cross-reactivity of hsp65 and proteoglycan link protein seems to be unlikely because only three residues of the seven amino acids are shared.

In human rheumatoid arthritis, a synovial fluid lymphocyte response against mycobacterial antigens[50-54] as well as the presence of IgG antibody to mycobacterial hsp65[55,56] has been reported. Several possible interpretations have been proposed, especially with respect to the role of hsp65 in human disease. Given the extensive homology (about 40% to 50% at the amino acid level) between the mycobacterial and human homologues, it was thought entirely likely that the human hsp65 homologue was the actual target of activated synovial T cells. Although this possibility was theoretically validated by the occurrence of immunologic cross-reactivity between mycobacterial and mammalian hsp65,[57-59] some recent reports do not support this hypothesis. Gaston and colleagues showed that T-cell clones recognizing mycobacterial

hsp65 did not cross-react with the human homologue.[60] Mycobacterial hsp65-reactive synovial T cells were not shown to be the dominant fraction of synovial T cells, especially at the chronic stage of rheumatoid arthritis.[52,54,61]

Alternatively, there could be an hsp65 cross-reacting host antigen other than human heat shock protein in the synovial tissue, for instance, proteoglycan. Primary sequence homology between *Escherichia coli* 40-kd hsp (dnaJ) and HLA-DR4 has been reported, as discussed later. Finally, it may be that the mycobacterial antigen, for some reason persisting in the synovial tissue, is the actual target of activated lymphocytes because the persistence of *Y enterocolitica* antigen in the joints of patients with reactive arthritis has now been clearly documented.[62] If this is the case, rheumatoid arthritis might be caused by *Mycobacterium* species by a mechanism similar to that for reactive arthritis. The fact that IgG is particularly low in glycosylated residues in both rheumatoid arthritis and tuberculosis[63] might affirm the causal relationship between these two diseases.

Bacterial or Viral Fc Binding Proteins and Rheumatoid Factors

Some bacteria possess proteins that bind to the human IgG Fc fragment. As information concerning the fine IgG specificity of these Fc binding proteins became available, interesting relationships between them and rheumatoid factors were apparent. Thus, Fc binding proteins such as staphylococcal protein A, streptococcal protein G, and T15 bind to the C_H2-C_H3 interface region of IgG, where most of the polyclonal rheumatoid factors derived from patients with rheumatoid arthritis react.[64-68] Protein A was also shown to stimulate rheumatoid factor production when cultured with human lymphocytes.[69]

An explanation for the relationship between rheumatoid factor and protein A (or other bacterial Fc binding proteins) may be that rheumatoid factors could be the anti-idiotypic antibody against autologous antibacterial Fc binding protein.[70,71] This mechanism could be referred to as "idiotypic mimicry" because the internal image of anti-Fc binding protein antibody should mimic the autologous IgG Fc region. Supporting this possibility, Oppliger and associates demonstrated that human rheumatoid factors bound to the Fab portion of chicken anti-protein A antibody.[72]

Herpesviruses also bind Fc binding proteins to the similar C_H2-C_H3 interface region of human IgG.[73-75] We have shown that human rheumatoid factors bind to Fab fragments of several monoclonal antibodies to the Fc binding protein of HSV-1 and HSV-2.[76,77] Subsequent epitope mapping using overlapping synthetic peptides confirmed that the epitopes for the monoclonal antibodies on the HSV Fc binding protein significantly overlap with the IgG binding site (R.C.W. and co-workers, unpublished data, May 1992). Other members of the herpesvirus family such as cytomegalovirus and Epstein-Barr virus have been more heavily implicated in the pathogenesis of rheumatoid arthritis. These viruses have also been known to possess Fc binding proteins.[78,79] The hypothesis that rheumatoid factor may be the anti-idiotypic antibody against anti-viral Fc binding protein requires further study.

Primary Sequence Homology Between HLA-DR4 Antigen and Infectious Agents

The susceptibility to rheumatoid arthritis is linked to HLA-DR4 and DR1 antigens. Primary sequence analysis revealed that these associated class II subtypes shared QRRAA or QKRAA at positions 70 to 74 within the third hypervariable region of the DRβ1 chain.[80] This region may be critical in the presentation of a hypothetical disease-associated peptide to T cells. An alternative possibility was proposed by Roudier and colleagues.[81] By computer analysis, these workers found a QKRAA sequence in gp110 of Epstein-Barr virus (Table 2)[82] and a 40-kd hsp of *E coli*, dnaJ.[83] They showed that a 15-mer peptide encompassing the QKRAA sequence derived from the DRβ1 chain or gp110 could be immunogenic for persons who did not possess this sequence, and remarkably the immune response was actually cross-reactive at both the T-cell and B-cell levels.[81] Whether immunization with the gp110 sequence could induce autoimmunity to an autologous DR molecule in DR4-positive persons remains to be established.

Conclusions

Molecular mimicry remains an attractive hypothesis to explain how disease-susceptible persons get disease by triggering events. Indeed, apparently meaningful primary sequence homology between autologous host tissues and various other extrinsic bacterial or viral antigens was found for many disorders, as discussed earlier. Much of this evidence still seems to be inconclusive, however, and such sequence homology could be merely a coincidence without any pathologic significance. In future studies, conformational similarity should be demonstrated rather than just a primary sequence homology for B-cell epitope mimicry. For T-cell cross-reactivity, the way in which the diseases involved must break T-cell anergy needs to be addressed. Much additional work is needed to determine whether molecular mimicry is actually pathogenetic or only an interesting hypothesis.

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Articles

Physician-Patient Sexual Contact
Prevalence and Problems

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To document the current prevalence of physician-patient sexual contact and to estimate its effect on involved patients, 10,000 family practitioners, internists, obstetrician-gynecologists, and surgeons were surveyed. Of the 1,891 respondents, 9% acknowledged sexual contact with 1 or more patients. Even in the unlikely case that none of the nonrespondents had sexual contact with patients, its prevalence among all 10,000 physicians surveyed would still be 2%. Of respondents, 23% had at least 1 patient who reported sexual contact with another physician; 63% thought this contact was "always harmful" to the patients. Almost all (94%) responding physicians opposed sexual contact with current patients; 37% also opposed sexual contact with former patients. More than half of respondents (56%) indicated that physician-patient sexual contact had never been addressed in their training; only 3% had participated in a continuing education course focusing on this issue. Clear and enforceable medical ethics codes concerning physician-patient sexual contact are needed, as well as preventive educational programs for medical schools and residency programs.

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Whatever houses I may visit, I will come for the benefit of the sick, remaining free of all intentional injustice, of all mischief and in particular of sexual relationships with both female and male persons, be they free or slaves.

HIPPOCRATIC OATH
4TH CENTURY BCE[1]

Sexual contact which occurs concurrent with the physician-patient relationship constitutes sexual misconduct. Sexual or romantic interactions between physicians and patients detract from the goals of the physician-patient relationship, may exploit the vulnerability of the patient, may obscure the physician's objective judgment concerning the patient's health care, and may ultimately be detrimental to the patient's well-being.

AMERICAN MEDICAL ASSOCIATION
COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS[2]

Concern about physician-patient sexual contact dates as far back as the Hippocratic treatise. Although the harm done by such contact has been well documented,[3-6] the prevalence of sexual contact between patients and physicians who are not psychiatrists has never been reliably established. Existing estimates are based on two small, geographically restricted surveys.[7,8] To document the current prevalence of physician-patient sexual contact, we surveyed randomly selected national samples of family practitioners, internists, obstetrician-gynecologists, and surgeons. We defined sexual contacts conservatively, excluding spouses, significant others, and sexual partners who later became patients. The survey was designed to address the following questions:

- How prevalent is physician-patient sexual contact?
- What are the opinions of physicians regarding sexual contact with patients?
- How are patients affected by sexual contact with physicians?

Methods

The 33-item anonymous questionnaire in this study was modified from the instrument developed by Gartrell and colleagues for 1985 and 1986 surveys of psychiatrists.[9,10] It contained 7 items on demographics, 4 on respondents' opinions, 2 on their education concerning physician-patient sexual contact, and 20 items on respondents' personal experiences with their patients. The questions on personal experience included four regarding patients who had been sexually involved with previous physicians and who were subsequently treated by the respondents. The remainder of the personal experience questions focused on the respondents' sexual contacts with their own patients. Physicians who answered affirmatively to sexual contact with patients were asked to specify the number of female and male patients with whom they had had sexual contact and were then asked a series of questions about their most recent sexual contact. These questions included a request to specify how long the physician had engaged in sexual contact with the patient and the nature of the medical treatment at the beginning of the sexual contact.

Sexual contact was defined in behavioral terms as physical "contact that arouses or satisfies sexual desire in the patient, physician, or both." Although the word "patient" referred to anyone the respondent had ever treated, physicians who had treated spouses, significant others, and sexual partners who later became patients were excluded from the pool of those who acknowledged sexual contact with patients. We decided on this exclusion because many physicians believe that treating one's spouse or significant other is not unethical. Therefore, our definition was conservative, and

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we studied only physician-patient sexual contact that began during or after medical treatment.

The study population consisted of 10,000 physicians in the United States randomly selected by specialty from the American Medical Association (AMA)'s master file of physicians—members and nonmembers—who had completed training and who were currently practicing clinical medicine. The sample included 3,000 family practitioners, 2,000 internists, 2,000 obstetrician-gynecologists, and 3,000 surgeons.

The questionnaire, a one-page cover letter containing the University of California, San Francisco, Committee on Human Research approval number, the university's Experimental Subjects Bill of Rights, and a stamped return envelope were mailed in May 1990. The questionnaire was preceded by an announcement postcard and followed by a reminder postcard. The cover letter explained the purpose of the study, the nature of the selection process, and the procedures for establishing complete confidentiality and anonymity. Because of the sensitive nature of the study—several questions pertained to conduct that is classified as felony sexual assault in some states—we did not code the questionnaires to identify nonrespondents. Consequently, the response rate could not be increased by follow-up phone calls or second mailings to nonrespondents. The respondents were asked to return the questionnaire by July 30, 1990.

TABLE 1.—*Characteristics of Respondents*

Characteristic	Respondents* No.	(%)
Sex (n = 1,888)		
Women	282	(15)
Men	1,606	(85)
Age (n = 1,882), yr†		
<35	324	(17)
35-44	800	(42)
45-54	393	(21)
55-64	348	(18)
>65	17	(1)
Board certification (n = 1,886)	1,615	(86)
Sexual orientation (n = 1,882)		
Heterosexual	1,848	(98)
Homosexual	19	(1)
Bisexual	15	(1)

*The total number of responses for each question varied because some respondents did not answer all questions.
†Median = 42 years.

The anonymous responses were keypunched and verified. Unless otherwise noted in the text, χ^2 tests (with continuity correction) were used in the analysis. To avoid the assumption of equal variance, t tests were computed by a separate variance method. Kruskal-Wallis and Mann-Whitney U tests were done for ordinal variables. Sample sizes reported for the statistical tests vary because of missing data on a number of variables. Quotations have been edited for grammar and spelling.

Results

Characteristics of Respondents

Of the 10,000 physicians surveyed, 1,891 (19%) completed and returned their questionnaires. The respondents included 679 family practitioners (23% response rate), 360 internists (18%), 344 obstetrician-gynecologists (17%), and 489 surgeons (16%). Twelve uncompleted questionnaires were returned with unusable or hostile comments.

Table 1 characterizes the respondents. The respondents were representative of US physicians in sex and age, although they were overrepresented in board certification.[11]

Sexual Contact With Patients

A total of 176 (9%) respondents acknowledged sexual contact with one or more patients (Table 2). An additional 56 reported that in the most recent case, their sexual partners later became their patients; these respondents were not counted as involved physicians even though more than half reported sexual contact with multiple patients.

Of those responding, 164 (10%) men and 12 (4%) women acknowledged sexual contact with a total of 332 patients. Of the contacts for which both the physician's and the patient's sex were specified, 89% occurred between male physicians and female patients, 6% between female physicians and male patients, 4% between male physicians and male patients, and 1% between female physicians and female patients.

Of involved physicians, 42% had sexual contact with more than one patient. The largest number of contacts reported by a physician was 11. When asked about their most recent patient contact, involved physicians indicated that the duration of the sexual involvement ranged from one "sexual encounter" (17%) to "more than five years" (15%). Nearly two thirds (66%) of those involved with one patient and more than half (58%) of those involved with two or more patients reported that the sexual relationship lasted less than 12 months; 72% indicated that the most recent contact involved a current patient; and 28% indicated that the most recent contact was a "former" patient, using their own definitions of "former." Two physicians who were involved with "former" patients wrote that the sexual contact began within three months of a surgical procedure. Of those whose most recent contact was a "former" patient, 35% had been involved with multiple patients. A few (7%) sought consultation with a colleague concerning their sexual involvement with the most recent patient.

TABLE 2.—*Physicians Acknowledging Sexual Contact With Patients, by Specialty (n = 176)*

Specialty	Acknowledge Contact With 1 Patient, No.	Acknowledge Contact With ≥ 2 Patients, No.	Total Acknowledging Contact, No. (% of Respondents in That Specialty)
Family practice (n = 679)	42	30	72 (11)
Internal medicine (n = 360)	14	7	21 (6)
Obstetrics-gynecology (n = 344)	15	19	34 (10)
Surgery (n = 489)	29	16	45 (9)
Specialty unspecified (n = 19)	2	2	4
Totals	102	74	176 (9)

TABLE 3.—*Respondents' Opinions Concerning Sexual Contact With Patients**

Statement	All Respondents Agreeing With Statement		Uninvolved Respondents Agreeing With Statement		Respondents Who Acknowledged Sexual Contact With ≥ 1 Patient Agreeing With Statement		P Value
	No.	(%)	No.	(%)†	No.	(%)†	
It is professionally acceptable to have sexual contact with a current patient (n = 1,882)	122	(6)	78	(5)	44	(25)	<.001
It is professionally acceptable for a physician to have sexual contact with a patient still taking medication prescribed by that physician (n = 1,870)	221	(12)	162	(10)	59	(34)	<.001
It is professionally acceptable to have sexual contact with a patient whose treatment has stopped and who has been referred to another physician (n = 1,855)	1,173	(63)	1,016	(60)	157	(90)	<.001
I favor state licensing board regulations prohibiting physician-patient sexual contact (n = 1,828)	987	(54)	939	(56)	48	(30)	<.001

*The total number of responses for each question varied because some respondents did not answer all questions.
†Overall, 1,715 respondents were uninvolved, and 176 were involved.

Respondents' Opinions Concerning Sexual Contact With Patients

Virtually all respondents (94%) opposed sexual contact with current patients. In addition, 37% opposed sexual contact with former patients. Respondents rejected the use of physician-patient sexual contact to treat sexual dysfunction (97%), to enhance the patient's self-esteem (98%), or to change a patient's sexual orientation (99%). Numerous respondents considered it highly inappropriate for the sexual contact to occur during a consultation. "The physician's genitals have no reason to be uncovered in the workplace," stated a 32-year-old female obstetrician-gynecologist. Some respondents described physician-patient sexual contact as a breach of trust. "The physician-patient relationship is based on trust, care, and the patient's best interest. Sexual contact exploits and violates that trust," said a 43-year-old male family practitioner. A 44-year-old male family practitioner made an analogy with incest: "Physician-patient sexual behavior is a form of incest: [it] breaks the trust bond and destroys boundaries." A 60-year-old family practitioner wrote that he learned about the negative effects of physician-patient sexual contact through personal experience: "This [relationship] was disturbed; I didn't understand how or to what depth until years later when she [the patient] committed suicide."

TABLE 4.—*Respondents Whose Patients Reported Sexual Contact With Another Physician (n = 424)*

Specialty of Respondent	Respondents in That Specialty Whose Patients Reported Sexual Contact With Another Physician	
	No.	(%)
Family practice	170	(25)
Internal medicine	68	(19)
Obstetrics-gynecology	119	(35)
Surgery	62	(13)
Specialty unspecified	5	--
Total	424	(23)*

*Percentage is of 1,882 respondents.

Physicians who had been sexually involved with patients were significantly more likely than uninvolved physicians to approve of sexual contact with patients and to oppose regulations prohibiting such contact (Table 3). Involved physicians were also more likely to approve of sexual contact when the physician "falls in love" with the patient (Mann-Whitney U = 166511, $P < .001$): 60% of involved physicians deemed it "sometimes appropriate" (compared with 34% of the uninvolved), and 9% of the involved group considered it "always appropriate" (compared with 2% of the uninvolved).

Concerning policy recommendations, more than half of respondents favored state licensing board regulations prohibiting physician-patient sexual contact. "State licensing prohibition would have deterred me [from dating a patient], and I would support it wholeheartedly," said a 40-year-old female family practitioner. "It [physician-patient sexual contact] should be forbidden in state license applications which doctors sign. There are too many temptations and vulnerable people out there for this subject to be closeted the way it has been," commented a 61-year-old male internist.

Medical Treatment of Sexual Partners

Of all respondents, 39% considered it professionally acceptable to become the physician of a current or former sexual partner. Men (41%) were more likely than women (26%) to consider it acceptable ($\chi^2 = 21.4$ [*df* 1], $P < .001$). However, a 32-year-old male family practitioner cautioned, "I feel that it would be very difficult to remain objective in medical treatment with a sexual intimate. Are we not taught the hazards of treating our own family members?"

Patients' Sexual Contacts With Other Physicians

Nearly a quarter of respondents (23%) had had at least one patient report sexual contact with another physician. The specialties of these respondents are shown in Table 4. A total of 1,085 female and 54 male patients reported such contact. Respondents who were involved sexually with their own patients were more likely than uninvolved respondents to hear from patients about their sexual involvement with other physicians (37% versus 21%; $\chi^2 = 20.9$ [*df* 1], $P < .001$).

When asked about the effect on their patients of sexual contact with other physicians, 63% of respondents (including 38% of involved physicians) indicated that it was "always harmful." No respondent found it "always helpful." Female respondents and respondents who were not sexually involved with their own patients were more likely to assess sexual contact with other physicians as harmful to their patients (Table 5). A 45-year-old male surgeon commented on the four patients he had seen who had been sexually involved with other physicians: "The patients felt betrayed, but most were too ashamed to press charges."

Respondents' Education Concerning Physician-Patient Sexual Contact

More than half (56%) of respondents indicated that physician-patient sexual contact had never been addressed during medical school or residency. Only 3% had participated in a continuing education course that addressed this issue. Some were frustrated about such lack of education. For example, a 42-year-old male family practitioner wrote, "During residency the issue was never addressed. When [as a resident] I fell in love with a patient and refused to continue as her doctor (before any sexual contact), the faculty would not discuss the matter with me." A 35-year-old female family practitioner commented that "there are too many complex issues of power/dependence, sexuality, trust, and confidentiality involved in the physician-patient relationship to allow [it] to develop into a romantic relationship. These are issues that medical school didn't address at all!"

TABLE 5.—*Adverse Effects of Physician-Patient Sexual Contact According to 424 Respondents Whose Patients Reported Sexual Contact With Other Physicians*

Respondents	Find Such Contact "Always Harmful" to Patient(s) No.	(%)	P Value
Female (n=68)	54	(81)	<.01
Male (n=356)	204	(60)	
Uninvolved respondents (n=360)	235	(68)	<.001
Involved respondents* (n=64)	23	(38)	

*Those who acknowledged sexual contact with their own patient(s).

Several younger respondents expressed gratitude that their training programs had addressed the issue. "I have been invited to become involved with female patients on three or four occasions, but medical school training helped me to handle these situations appropriately," wrote a 26-year-old male family practitioner.

Comment

Nearly one of ten physicians responding to this anonymous survey acknowledged sexual contact with their own patients. The prevalence of physician-patient sexual contact among our male respondents is consistent with a previous smaller study.[7] Our prevalence of sexual contact between women physicians and their patients is higher than previously reported. Only one of the California and New York women physicians surveyed by Perry[8] in 1976 had engaged in erotic contact with a patient.

While our response rate of 19% may limit our ability to generalize about physician-patient sexual contacts, inquiring about behavior that might be punishable as felony sexual assault may have diminished our returns. Some respondents commented that no physician living in a state that actively prosecuted physician-patient sexual involvement would ever return such a questionnaire. Other respondents may not have reported sexual involvement with their own patients out of a concern that such information might damage the credibility of the profession. The percentage acknowledging sexual contact with patients might have been higher if the physicians who received questionnaires had felt less inhibited. Even in the unlikely case that none of our nonrespondents had had sexual contact with patients, the prevalence of such contact among all 10,000 physicians surveyed would still be 2%. Furthermore, 23% of respondents reported sexual contact between their patients and other physicians—which suggests that self-reporting may underestimate the true prevalence of this problem.

Sexual contact between physicians and their current patients violates the fiduciary nature of the physician-patient relationship, which requires physicians to act for the benefit of patients who entrust their care to them.[12] When seeking medical care from physicians, patients are vulnerable because of their illnesses and dependent on their physician's medical expertise. To receive the care they need, patients must provide intimate information in the medical history, undress for a physical examination, and, for surgical procedures, allow their physician to violate bodily integrity. During this process, patients develop feelings of trust and respect for their physicians, as well as gratitude for the physicians' willingness to listen and ability to heal. Because feelings of trust, dependency, gratitude, and intimacy are inherent in the physician-patient relationship, patients may find it difficult to decline sexual initiatives from their physicians. Some patients, because of their vulnerability, may interpret their physician's professional caring as personal intimacy and even initiate sexual advances. It is the physician's responsibility, however, to prevent the harm that may result from physician-patient sexual contact.[12]

Sexual contact between physicians and their current patients may seriously harm patients.[5] In our study, two thirds of uninvolved physicians whose patients reported sexual contact with other physicians thought that such contact was "always harmful." This belief that sexual contact with physicians can harm patients is supported by the recent Ontario College of Physicians and Surgeons Task Force on Sexual Abuse of Patients.[5] The task force documented 174 cases of "clear substantive abuse" of patients who are sexually involved with physicians. Many of these patients felt exploited or betrayed when the sexual contact ended. Some reported that they were unable to trust subsequent physicians. Because a sexual relationship may interfere with professional objectivity, a patient who is sexually involved with her or his physician may receive inadequate medical care, especially with issues regarding pregnancy, sexually transmitted diseases, or psychologic health.[3] The task force concluded that these violations of trust in the physician-patient relationship were "devastating for the victim, usually in many aspects of her or his life, for the families affected, for the trust we place in the medical profession and for society as a whole."[5] We concur with most of our respondents, the AMA Council on Ethical and Judicial Affairs, and the Ontario College of Physicians and Surgeons that sexual contact between physicians and current patients is unethical.

Although almost all respondents in our study condemned sexual contact with current patients, they disagreed about the appropriateness of sexual contact between physicians and former patients. Physician-patient sexual contact was thought permissible by 63% if treatment had stopped and the patient had been referred to another physician. Some indicated that feelings of trust, dependency, or gratitude do not arise in all patient-physician relationships or may diminish over time. Even though our data do not support the contention that physician-patient sexual contact generally leads to long-term relationships—43% of involved physicians had sexual contact with more than one patient; most of these physician-patient sexual relationships lasted less than 12

months—several respondents cited personal knowledge of successful long-term relationships between physicians and their former patients. Others thought that physician-patient relationships should be judged on a case-by-case basis. They suggested that some patients could make autonomous choices to have sexual relationships with former physicians and would be no more likely to be harmed than by any other sexual partners.

The remaining 37% of respondents opposed sexual contact with former patients. The AMA Council on Ethical and Judicial Affairs agrees: "Sexual or romantic relationships with former patients are unethical if the physician uses or exploits trust, knowledge, emotions, or influence derived from the previous professional relationship."[2] That patients have been seriously harmed by sexual relationships with their former physicians has been documented.[5,6] Such relationships need to be considered carefully.

The issue is not how inconsequential the physician considered a previous interaction but, rather, how important the patient considered it. A patient's problem may seem routine or trivial to the physician but not to the patient. Suppose a physician meets a patient socially two years after a single clinic visit. The physician may have forgotten the original care, but can we be certain that the patient's dependency and gratitude have been extinguished, or that he or she is no longer vulnerable? For many patients, feelings that arise in a therapeutic relationship persist long after the episode of medical care.[3] Furthermore, in a brief visit most physicians are unlikely to have time to determine whether a patient had some special vulnerability, such as a history of sexual abuse, that might complicate relationships with authority figures. Thus, it may be impossible for physicians to be sure that they are not taking advantage of a previous physician-patient relationship to gratify their own needs.

For physicians to avoid harming patients, we suggest that they consider two guidelines before becoming sexually involved with a former patient. First, the professional relationship must have been terminated with no intent of future sexual involvement or a continuing social relationship. By termination, we mean that in the previous two years, there have been no office visits, no prescriptions written, no telephone consultations, and no return appointment reminder postcards.

We agree with the recommendation of the Ontario College Task Force[5] that at least two years must have elapsed since the last episode of patient care, with no social contact in the interim. The key issue is not time but, rather, a discontinuous relationship. A dating relationship between a physician and patient that began a month after termination of care would be inappropriate, therefore, even if the involved parties had refrained from consummating it for two years.

Second, the physician and former patient should meet again in a context entirely unrelated to the previous professional encounter. This helps ensure that the former patient is no more likely to be harmed than by any other possibly sexual relationship.

It is difficult to be objective during the early phases of a new relationship. Thus, both the physician and the patient may wish to discuss the incipient involvement confidentially with an advisor who will provide an honest appraisal of the potential harm to the patient, the physician, and the medical profession. Such counsel is a safeguard for physicians who might be inclined to act only on their impulses. Discussing such an intimate decision with an advisor—even anonymously—may seem intrusive, but it may remind physicians that such decisions are not completely private if they undermine public trust in the profession.

An unexpected finding in our study was that many respondents indicated that they treated their spouses, significant others, and former sexual partners. We did not ask whether such treatment involved serious medical illness. Although treating intimates for major medical problems is not unethical, it is unwise.[13] As one respondent wrote, "You can't be objective when you are emotionally involved."

Our finding that physician-patient sexual contact had never been addressed during the medical training of more than half of our respondents is disturbing. The need for education on this issue is evidenced by the fact that 23% of respondents had encountered patients who had been sexually involved with other physicians. The Ontario College of Physicians and Surgeons' Task Force[5] recommends comprehensive training on physician-patient sexual contact. We think that curricula should include these topics:

- Recognizing and managing nontherapeutic emotional responses to patients;
- Implications of the power dynamics between physicians and patients and women and men;
- The adverse effects of physician-patient sexual contact;
- The effect of physician-patient sexual contact on public trust in the medical profession;
- The legal implications of physician-patient sexual contacts (civil and criminal statutes).

Our study demonstrates that physician-patient sexual contacts occur despite professional ethical prohibitions. The potential for harm to patients from such contacts is serious. Physician-patient sexual involvement ultimately affects the credibility of the entire medical profession. We urge medical schools, residency programs, and continuing education courses to include teaching about this topic. A substantial educational effort will be required to prevent nearly 10% of the next generation of physicians from compromising patients' welfare and public trust in the profession.

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Articles

Mycobacterium avium Complex and *Mycobacterium tuberculosis* in Patients Infected With the Human Immunodeficiency Virus

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Primary care physicians play an important role in identifying and treating bacterial infections in adults infected with the human immunodeficiency virus (HIV). *Mycobacterium avium* complex and *Mycobacterium tuberculosis* are pathogens that can cause systemic or local infection in these patients. We review the epidemiology, pathogenesis, clinical presentation, and principles of treatment for these two mycobacterial pathogens. Because *M tuberculosis* disease is preventable and curable and yet communicable, physicians should maintain a high degree of suspicion for tuberculosis in HIV-infected adults. In comparison, the goal of treating *M avium* complex in patients with advanced HIV disease is to reduce constitutional symptoms and improve survival.

(Kerlikowske KM, Katz MH: *Mycabacterium avium* complex and *Mycabacterium tuberculasis* in patients infected with the human immunodeficiency virus. West J Med 1992 Aug; 157:144-148)

Mycobacterium avium complex and *Mycobacterium tuberculosis* are the most common mycobacteria causing disease in adults infected with the human immunodeficiency virus (HIV). The incidences of infection with these mycobacterial pathogens have steadily increased since the beginning of the HIV epidemic.[1,2] Diagnosing, treating, and preventing these diseases is an increasingly important aspect of caring for HIV-infected patients. We review the epidemiology, pathogenesis, clinical manifestations, and treatment of these two mycobacterial diseases in HIV-infected patients.

Mycobacterium avium Complex

Epidemiology and Pathogenesis

Mycobacterium avium complex accounts for 97% of the nontuberculous mycobacteria identified in patients with the acquired immunodeficiency syndrome (AIDS) and is the most common cause of bacteremia and intrahepatic lesions in patients with AIDS.[3,4] The percentage of AIDS cases in the United States with nontuberculous mycobacteria increased from 5.5% in 1987 to 7.6% in 1990.[1] Clinic-based studies have shown an even higher cumulative incidence of disseminated *M avium* complex, ranging from 18% to 23%. Because disseminated *M avium* complex occurs relatively late in the course of HIV disease, the increased incidence of this infection may be due to the fact that HIV-infected patients are living longer because of better treatment against HIV and opportunistic infections.

The clinical significance of *M avium* complex in HIV-infected patients has been debated. It was initially regarded as a commensal of the gastrointestinal and pulmonary tracts that disseminated in some patients with advanced AIDS but did not contribute to overall mortality. More recent studies have shown that mortality is increased in AIDS patients who have disseminated *M avium* complex. A recent study showed a median survival of 4 months in AIDS patients with disseminated *M avium* complex compared with 11 months in controls without the complex.[5] Moreover, survival when *M avium* complex is the index AIDS diagnosis has been reported to be shorter (median 4.2 months) than when other opportunistic infections such as *Pneumocystis carinii* pneumonia (median 14.7 months) or esophageal candidiasis (median 15.9 months) are the index AIDS diagnosis.[6]

Unlike many of the opportunistic infections that occur in AIDS patients, disseminated *M avium* complex is probably not due to the reactivation of a latent infection.[1] The acquisition of this pathogen appears to result primarily from ingesting water or soil containing *M avium* complex.[7] The pulmonary tract may become infected by aspiration from an infected gastrointestinal tract or possibly by the inhalation of aerosols containing the organism.

It is not known what percentage of patients with localized infection will progress to disseminated disease, nor is it known whether disseminated disease can occur without previous localized infection. Retrospective studies have shown that about 30% to 35% of patients with disseminated disease have infection of the gastrointestinal or pulmonary tracts before dissemination.[8,9] Prospective studies are needed to determine more accurately the relative contribution of respiratory and gastrointestinal tract infection to the dissemination of *M avium* complex.

Clinical Presentation and Diagnosis

Disseminated Mycobacterium avium *complex.* In patients with disseminated *M avium* complex, the diagnosis is made an average of 9 to 12 months from the development of an index AIDS diagnosis.[10,11] About 70% of patients when diagnosed with disseminated disease will have $CD4^+$ lymphocyte counts of less than 50 cells $\times 10^6$ per liter.[12] Only 5% to 6% of patients will have disseminated *M avium* complex as their index AIDS diagnosis. The risk of mycobacterial bacteremia increases each year following an AIDS diagnosis, with *M avium* complex bacteremia developing in about 15% of AIDS patients per year after AIDS has been diagnosed.[13]

Disseminated infections include those cases in which *M avium* complex is cultured from usually sterile tissue—blood, liver, bone marrow, lymph node, cerebrospinal fluid,

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
HIV = human immunodeficiency virus

pleural fluid, and peritoneal fluid—or, less commonly, from biopsy specimens of disseminated skin lesions. Patients frequently present with constitutional symptoms—fever, weight loss, sweats, anorexia, malaise—and less often with abdominal pain and diarrhea. Hepatosplenomegaly and lymphadenopathy are present in about 50% of patients; anemia (hemoglobin less than 100 grams per liter [10 grams per dl]) and increased alkaline phosphatase activity are also common. Patients with abdominal pain and diarrhea may have intra-abdominal lymphadenopathy. Although these symptoms, signs, and laboratory abnormalities are common in disseminated *M avium* complex, they are not sensitive or specific indicators of disease.

Blood cultures are the most sensitive test to diagnose disseminated *M avium* complex, yielding positive results on average in 14 days (range, 7 to 51 days).[14] In patients with persistent *M avium* complex bacteremia, the first culture is positive 91% of the time; repeating the culture increases the yield to 98%.

There is less information on the diagnostic yield of tissues other than blood when patients do not have mycobacteremia. In a retrospective study of patients who had blood and bone marrow specimens cultured for *M avium* complex, bone marrow biopsies revealed *M avium* complex infection in 26% of cases without isolation of the organism from blood.[15] Culture of liver biopsy specimens in AIDS patients with alkaline phosphatase activity greater than 300 units per liter (normal 30 to 120) and fever of unknown origin has a sensitivity of 75% to 86%. Mycobacteria account for 75% to 85% of the diagnoses made by liver biopsy, and *M avium* complex accounts for 60% to 75% of the total mycobacterial diagnoses.[16] A liver biopsy should be considered for those patients with unexplained fever, blood cultures negative for *M avium* complex, and alkaline phosphatase levels at least two to three times the upper limits of normal.

Localized infections with Mycobacterium avium *complex.* Localized infections (pneumonia, skin nodules, and diarrheal syndromes) tend to occur in HIV-infected patients with better immune function.[3] Pneumonia due to *M avium* complex has no specific radiologic pattern. Localized skin lesions usually occur with lymphadenitis. Patients with gastrointestinal *M avium* complex who present with large-volume diarrhea and steatorrhea often have localized infection in the small intestine; biopsy specimens of the duodenum may show numerous mycobacteria. Patients with gastrointestinal *M avium* complex who present with left lower quadrant pain and small-volume diarrhea usually have infection localized to the colon; rectal biopsy specimens or stool cultures may show numerous mycobacteria.

Principles of Treatment

With recent information on the contribution of *M avium* complex to morbidity and mortality in patients with AIDS, there has been a renewed interest in treating patients with disseminated disease.[17-19] At present, however, the only published studies evaluating the efficacy of the treatment of disseminated *M avium* complex in AIDS patients are uncontrolled, nonrandomized studies. Retrospective studies have shown that patients who are treated with three or more antimycobacterial drugs have improved survival.[5,11] Because treatment regimens varied, however, the optimal treatment regimen to decrease morbidity and prolong survival could not be determined.

Most of the drug regimens currently being given follow the guidelines for the treatment of *M avium* complex infections in patients without AIDS and use at least three to four antimycobacterial drugs for at least 18 to 24 months (Table 1).[17-19] Table 2 lists the drugs currently being used and common side effects from those medications. In addition, there are ongoing clinical trials using macrolides (clarithromycin and azithromycin) as a single agent to treat disseminated *M avium* complex. Studies have shown that administering these macrolides for four to six weeks can reduce *M avium* complex counts in the blood of AIDS patients.[20,21] Whether the long-term administration of macrolides will maintain reduced *M avium* complex counts in the blood and improve survival is not known.

TABLE 1.—*Principles of Treotment of Infection With* Mycobacterium avium *Complex*

Treatment recommended
Documented disseminated *Mycobacterium avium* complex in symptomatic and asymptomatic patients
Lung infiltrate with documentation of *M avium* complex in sputum or bronchoalveolar lavage (BAL) without evidence of other pathogens that could account for the infiltrate
Localized skin nodules with lymphadenitis
Treatment not recommended
Asymptomatic patients with a normal chest x-ray film and *M avium* complex in sputum or BAL
Asymptomatic patients with *M avium* complex recovered from stool
Treatment controversial
Patients with diarrhea who have *M avium* complex cultured from stool or bowel
Treatment guidelines
Begin therapy with a 4-drug oral regimen (ethambutol, rifampin or rifabutin, ciprofloxacin, and clofazimine)
If drug toxicity occurs from 1 or more oral agents, attempt to maintain the patient on at least 3 antimycobacterial drugs
If there is no response to therapy in 4 to 6 weeks, consider adding an aminoglycoside to oral therapy or changing to clarithromycin

Standard mycobacterial sensitivity testing cannot be used to evaluate the susceptibility of these organisms to medication. Minimal inhibitory concentration testing to select antimycobacterial therapy is still investigational and not recommended at this time because methods have not been shown to correlate with the clinical response to therapy.

Efficacy and Prognostic Factors

The best measures of efficacy of antimycobacterial treatment are the resolution of constitutional symptoms and a decreased bacterial burden. With a four-drug oral regimen, about 75% of AIDS patients with disseminated *M avium* complex were asymptomatic at 12 weeks, and about 86% had negative blood cultures.[17] In those patients who respond to treatment, systemic symptoms—fever, sweats, lethargy—usually resolve within four weeks.[19] Treatment has not been found to reverse weight loss or decrease transfusion requirements.

In those institutions where quantitative mycobacterial

TABLE 2.—*Daily Drug Doses for the Treatment of* Mycobacterium avium *Complex**

Drug	*Oral Dose/d*	*Intravenous Dose/d*	*Side Effects*
Ethambutol HCl†	15 mg/kg	--	Decreased visual acuity, abdominal pain, nausea
Rifampin‡	10 mg/kg	10 mg/kg	Rash, nausea, vomiting, hepatitis, thrombocytopenia, renal failure
Ciprofloxacin	750 mg×2	750 mg×2	Abdominal pain, nausea, vomiting, rash, increased creatinine, headache, lightheadedness
Clofazimine	100 mg	--	Skin discoloration, rash, abdominal pain, nausea, vomiting
Amikacin	--	7.5 mg/kg	Nephrotoxicity, ototoxicity
Streptomycin	--	10-15 mg/kg	Ototoxicity, nephrotoxicity
Experimental			
Rifabutin	300-600 mg	--	Diarrhea, nausea, vomiting, rash, leukopenia, hepatitis
Clarithromycin	2,000 mg	--	Hepatitis
Azithromycin	500 mg	--	Diarrhea

HCl = hydrochloride

*From Hoy et al,[17] Chiu et al,[18] Kemper et al,[19] and Dautzenberg.[20]
†Maximum dose, 1,000 mg/d.
‡Maximum dose, 600 mg/d.

blood cultures can be done, decreasing bacterial counts can be used as an indicator of response to treatment. Routine mycobacterial blood cultures are not recommended to monitor response to treatment because the persistence of the organism in cultures does not mean there was not a decrease in bacterial counts.

There is limited information on factors that affect the natural history of disseminated *M avium* complex. Anemia (hematocrit less than 0.25 [25%]) has been reported to be a prognostic indicator of poor survival in patients with disseminated *M avium* complex.[22] Elevated alkaline phosphatase levels are also associated with decreased survival, which may indicate an increased bacterial burden of *M avium* complex in liver and bone marrow.[11]

Surveillance and Prevention

Blood cultures are indicated in HIV-infected patients with signs and symptoms consistent with disseminated *M avium* complex, especially in those patients with $CD4^+$ counts of less than 100 cells $\times 10^6$ per liter. For asymptomatic patients, the diagnostic yield per blood culture is too low to warrant surveillance cultures. In one study done to evaluate the usefulness of screening mycobacterial cultures, about one in five patients tested had a blood culture positive for *M avium* complex. Those with positive blood cultures all had signs or symptoms of disseminated *M avium* complex and $CD4^+$ lymphocyte counts of less than 100 cells $\times 10^6$ per liter.[1,13]

Whether the identification of *M avium* complex in stool or sputum specimens is a predictor of subsequent dissemination is being investigated prospectively. Therefore, screening stool and sputum specimens for *M avium* complex for localized infection in asymptomatic patients is not currently recommended. Trials of primary prophylaxis with clofazimine and rifabutin to prevent disseminated *M avium* complex in patients with low $CD4^+$ lymphocyte counts are ongoing.

In summary, disseminated *M avium* complex is a common infection in patients with advanced HIV disease that causes debilitating symptoms and shortens survival. Because some patients will respond to treatment with a reduction in constitutional symptoms and improved survival, therapy with at least three antimycobacterial agents should be offered to HIV-infected patients with disseminated *M avium* complex.

Mycobacterium tuberculosis

Epidemiology and Pathogenesis

The increased incidence of tuberculosis in the United States in the past five years is primarily due to the HIV epidemic. Tuberculosis is especially common among HIV-infected groups with a recognized high prevalence of *Mycobacterium tuberculosis* infection—African Americans, Hispanics, and injection drug users.[23] Nationally, tuberculosis develops in 4% of AIDS patients[24]; in some urban areas, as many as 28% of patients with tuberculosis are HIV-positive.[25] Based on this observation, HIV testing is recommended for all cases of tuberculosis in areas where there is a high prevalence of HIV infection.[26]

As in immunocompetent adults, 90% of cases of tuberculosis in those infected with HIV are due to a reactivation of latent *M tuberculosis* infection, with 10% of cases due to primary infection. The lifetime risk of tuberculosis developing in tuberculin reactors is at least twofold to threefold greater in HIV-infected patients than in tuberculin reactors who are not HIV-infected, or about a 30% lifetime risk. The rate of conversion to tuberculosis for HIV-infected adults with positive tuberculin reactions is 7% per year for the first two years compared with 0.1% per year for non–HIV-infected adults with a normal chest roentgenogram.[27]

Patients with advanced HIV disease who have had exposure to tuberculosis are at an increased risk for tuberculosis developing compared with persons not infected with HIV.[28] Outbreaks of tuberculosis have been reported in group residences and hospitals that care for patients with advanced HIV disease.[28,29] These observations suggest that recently acquired tuberculous infections can progress rapidly to active disease in patients with advanced HIV disease.

Clinical Presentation and Diagnosis

Most cases of tuberculosis in HIV-infected persons occur before a diagnosis of AIDS has been made. Less than 20% of diagnoses are made after an AIDS diagnosis. Pulmonary disease is the most common manifestation of tuberculosis.

Patients infected with HIV who are not severely immunocompromised usually present with clinically typical pulmonary tuberculosis with apical infiltrates or cavitation on chest roentgenograms. Those who are severely immunocompromised often present with clinically atypical pulmonary and extrapulmonary *M tuberculosis*. Chest roentgenograms of these patients may show hilar or mediastinal adenopathy (or both), middle or lower lobe involvement, diffuse interstitial or miliary disease, or no abnormalities.[26]

Extrapulmonary disease occurs in 50% to 60% of HIV-infected patients with *M tuberculosis* disease, and half of these patients also have pulmonary tuberculosis. Fever and lymphadenitis are the most common presentation of extrapulmonary tuberculosis. Patients with extrapulmonary disease and no evidence of pulmonary involvement tend to have lower mean $CD4^+$ lymphocyte counts (153 cells $\times 10^6$ per liter) than do patients who present with only pulmonary tuberculosis (326 cells $\times 10^6$ per liter).[25]

Evidence of infection with *M tuberculosis* in HIV-infected patients has been defined as 5 mm or greater of induration in reaction to tuberculin antigen.[30] The likelihood of a positive reaction decreases as the length of time after an AIDS diagnosis increases. In one study, patients in whom AIDS developed two years after their episode of pulmonary tuberculosis all had a positive tuberculin reaction (≥ 10 mm of induration) when they were diagnosed with pulmonary tuberculosis. Only 33% of patients who were diagnosed with tuberculosis concurrently with or after their AIDS diagnosis had a positive tuberculin reaction, however.[26] This decrease in tuberculin positivity is thought to be due to depressed cell-mediated responses that occur as $CD4^+$ lymphocyte counts decline. For this reason, some have argued that the cutoff point for infection with *M tuberculosis* should be lowered to 2 mm in patients with HIV infection.[31] At present there are insufficient data on the risk of tuberculosis in HIV-infected adults by tuberculin reaction sizes to make this recommendation.

TABLE 3.—*Treatment Guidelines for* Mycobacterium tuberculosis*

Treatment Period	*Oral Dose/d*
First 2 months of therapy	Isoniazid, 300 mg Rifampin, 600 mg† Pyrazinamide, 20-30 mg/kg Ethambutol hydrochloride, 25 mg/kg‡
Last 4 to 7 months of therapy or for 6 months after 3 negative cultures	Isoniazid, 300 mg Rifampin, 600 mg

*From the Centers for Disease Control.[26]
†Dose should be 450 mg/d if patient weighs ≤ 50 kg.
‡Administer when isoniazid resistance is likely.

Although infection with *M tuberculosis* is indicated by a positive tuberculin reaction, isolating *M tuberculosis* from cultures is required to document disease. The sensitivity of acid-fast bacilli (AFB) smears and cultures is the same in HIV-infected patients as in adults not infected with HIV.[25,32] Smears of sputum are positive for AFB 47% to 60% of the time, and cultures are positive 88% to 93% of the time.[25] Cultures of lymph node, bone marrow, and urine also have a high diagnostic yield.

Principles of Treatment

The Centers for Disease Control (CDC) recommendations for the treatment of tuberculosis in HIV-infected patients are listed in Table 3.[26] These guidelines are the same as those for persons not infected with HIV except that a longer period of treatment is recommended. Although the CDC recommends between 9 and 12 months of treatment, retrospective studies suggest that 6 months of treatment is probably as effective as 9 to 12 months. This assumes that the *M tuberculosis* organism isolated is not isoniazid- or rifampin-resistant and that patients can complete two months of therapy with four antimycobacterial drugs and then four months with isoniazid and rifampin for a total of six months of therapy.

Multidrug-resistant tuberculosis has been reported in HIV-infected adults.[33-36] Outbreaks of multidrug-resistant tuberculosis underscore three important points:

- That HIV-infected adults with advanced disease are susceptible to a rapid progression to clinical tuberculosis after infection with *M tuberculosis*,
- That multidrug-resistant tuberculosis has the potential to spread rapidly to health care professionals and persons in group residences with exposure to infectious adults, and
- That drug-susceptibility testing must be done on initial cultures of *M tuberculosis* organisms isolated from all HIV-infected adults.

A high index of suspicion for multidrug-resistant tuberculosis should be maintained, especially when sputum smears remain positive despite therapy for more than three months. In cases of drug resistance, therapy for at least 12 months is recommended and consultation with a specialist is advisable.

Outcome

Sputum conversion occurs at the same rate in HIV-infected patients as in HIV-seronegative patients, with 80% of patients with negative cultures at three months. The reported relapse rate is low at 2% to 5% after six to nine months of therapy.[23] Survival from tuberculosis is decreased in patients with advanced AIDS compared with HIV-infected patients diagnosed with tuberculosis before an index diagnosis of AIDS.[23] The incidence of adverse drug reactions is increased in HIV-infected patients, ranging from 18% to 26%. Patients with AIDS tend to have a higher incidence of drug reactions to antituberculous drugs than HIV-infected patients in whom AIDS has not yet developed.

Prevention

All HIV-infected patients should have a tuberculin skin test and skin test antigens (mumps or tetanus toxoid) applied by the Mantoux method at the time of tuberculin skin testing early in the course of HIV disease. If the initial tuberculin test is negative and the patient is not anergic, the tuberculin skin test should be repeated yearly until either anergy develops or the patient has a positive reaction. If the tuberculin reaction is 5 mm or more of induration, then active disease should be excluded by obtaining a chest roentgenogram and examining peripheral lymph nodes for evidence of infection. In patients who are symptomatic (fever and cough), three sputum specimens for AFB should also be collected. Lymph nodes should be aspirated if signs of infection are present. If active disease is excluded, isoniazid (300 mg) should be administered for 12 months.[30]

Anergic HIV-infected patients with a history of a positive tuberculin test or a chest roentgenogram suggesting previous *M tuberculosis* infection and no history of prophylaxis should be given 12 months of isoniazid therapy after pulmonary and extrapulmonary disease has been excluded. Anergic HIV-infected patients at high risk for *M tuberculosis* infection (injection drug users, prisoners, homeless persons, migrant laborers, and persons born in countries in Asia, Africa, and Latin America) and in whom the tuberculin status is unknown should be considered for preventive therapy.[37,38] Because the recommendations for isoniazid prophylaxis are different for HIV-infected patients, patients with a positive tuberculin reaction whose HIV status is not known should be offered an HIV test if they are from an area of high prevalence of HIV disease.

The efficacy of isoniazid therapy in reducing the incidence of tuberculosis in HIV-infected patients is being evaluated in clinical trials. Data collected in uncontrolled studies suggest that preventive therapy with isoniazid is effective.[27,28] Because HIV-infected patients with tuberculosis respond well to treatment with antimycobacterial drugs, it is assumed that isoniazid prophylaxis will prove to be efficacious when tested in controlled trials.

In summary, tuberculosis is common in HIV-infected patients, and its incidence will probably continue to increase as the prevalence of HIV disease rises. *M tuberculosis* disease is a unique infection in patients with AIDS because it is communicable and virulent and yet preventable and curable. In addition, because tuberculosis can be the first clinical manifestation of cellular immunodeficiency, its recognition allows for HIV testing and staging and the subsequent initiation of antiviral therapy.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Articles

Quantitative Quality Assurance in a Community Hospital Pediatric Intensive Care Unit

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Unbiased, objective evaluations of quality of care are preferred over subjective evaluations. We observed 681 admissions to a pediatric intensive care unit of a community hospital from 1989 through 1990 for outcomes and physiologic profiles of the patients on the admission day using the Pediatric Risk of Mortality score to assess severity of illness. Mortality adjusted for severity of illness was compared with that predicted from a pediatric intensive care unit of a tertiary medical center: 32.6 deaths were predicted based on the physiologic profiles, and 23 occurred. The number of outcomes and their distribution according to mortality risk indicated close agreement between observed and predicted results. Thus, a quality-assurance technique developed in tertiary care centers can be used to indicate a comparable level of care in a community hospital.

(Frank BS, Pollack MM: Quantitative quality assurance in a community hospital pediatric intensive care unit. West J Med 1992 Aug; 157:149-151)

Claims of providing quality pediatric intensive care are common but difficult to prove. Subjective medical record reviews of morbidity and mortality are a traditional method of assessing care but are of limited value. Physicians using subjective criteria often disagree about the quality of care, and subjective case reviews may not detect even gross problems of quality.[1,2] Furthermore, in a community hospital where the number of physicians is limited, the persons qualified to perform subjective case reviews are usually involved with the patients' care. An objective comparison of the outcomes of an individual pediatric intensive care unit (PICU) with an accepted standard avoids these problems. The Pediatric Risk of Mortality (PRISM) score assesses severity of illness (mortality risk) based on patients' physiologic status on the day of admission.[3-5] The PRISM score has successfully predicted mortality in samples of PICU patients by adjusting for differences in age and severity of illness. These previous applications included only tertiary care centers. We applied the PRISM score to a PICU in a community hospital to demonstrate its applicability to community hospital settings.

Patients and Methods

The study population came from a PICU at Washoe Medical Center in Reno, Nevada. Reno has a population of about 150,000, and the PICU referral population is about 250,000. Washoe Medical Center is a 400-bed hospital with 30 pediatric beds. There is 24-hour availability of respiratory therapy, radiology (including computed tomography and nuclear medicine), laboratory, and pharmacy services. Daily visits are made by nutritionists and social workers. There are no house-staff physicians. Although at least one emergency department physician is present in the hospital 24 hours per day, the physician has no direct inpatient responsibility and is typically not relied on for pediatric patient care including cardiac arrests.

The PICU has six beds including one isolation room. In the period January 1, 1989, through December 31, 1990, the average daily census in the PICU was 4.1 patients. A core staff of 12 registered nurses with in-house PICU training and an average of 4.7 years of PICU experience work 12-hour shifts. Protocols allow nurses to apply bag-and-mask ventilation and administer intravenous drugs during emergencies. Other emergency situations are handled by the PICU physician by telephone until the physician arrives on the scene. Respiratory therapists are drawn from a hospital-wide pool and have various degrees of pediatric experience. They often have responsibilities in other hospital areas at the same time as they have responsibilities in the PICU.

Patients are admitted and managed by primary care physicians and subspecialists as well as a full-time medical director, when consulted. The director, who has been fellowship-trained and certified in Pediatric Critical Care Medicine, is available within 20 minutes in the PICU. During the absence of the director, coverage is provided by a pediatrician with extra PICU training. Other pediatric subspecialists available include specialists in pediatric cardiology, nephrology, endocrinology, infectious disease, neurology, allergy-immunology, and neonatology.

All PICU admissions from 1989 to 1990 were reviewed. Admissions of adults to the PICU when the adult intensive care unit was full were not included. Twenty-three patients were transferred to other facilities for therapy not available in this hospital. One of the transfers died at the receiving facility. Descriptive data included age, diagnoses, and use of the operating room on the day of admission.

Physiologic status was assessed with the PRISM score. The PRISM score uses abnormalities of 14 routinely measured variables—systolic and diastolic blood pressures, heart rate, respiratory rate, the ratio of Pa_{O_2} to the fraction of inspired oxygen, Pa_{CO_2}, Glasgow coma score, pupillary reactions, prothrombin time or partial thromboplastin time, and serum levels of total bilirubin, potassium, calcium, glucose, and bicarbonate. Age-adjusted abnormality ranges for

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ABBREVIATIONS USED IN TEXT

PICU = pediatric intensive care unit
PRISM = Pediatric Risk of Mortality

each variable are assigned scores that reflect the mortality risk of the patient on a logistic scale. The validity of the PRISM score has been assessed by a prediction of mortality adjusted by severity of illness in PICUs in tertiary center hospitals. Thus, mortality for PICU populations has been predicted based solely on physiologic variables and age without adjustments for other variables in each case. Mortality risk was calculated as follows:

$$R = 0.207 \times \text{PRISM} - 0.005 \times \text{Age in Months} - 0.433 \times \text{OR Status} - 4.782$$

where R is the risk and OR Status = 1 for patients who went to the operating room on the day of admission and 0 for those who did not and

$$\text{Probability of PICU death} = [exp\ (R)]/[1 + exp\ (R)].$$

Patients were grouped into mortality risk intervals (0% to 5%, 5% to 30%, and more than 30%), and the number of outcomes (survival or death) within each interval were calculated. The observed outcomes were compared with those predicted by the PRISM score using a goodness-of-fit χ^2 test.[6] Therefore, both the numbers and the distributions of outcomes were assessed. The transferred patients were included with their eventual outcome for two reasons. First, this PICU recognizes that its expertise cannot be maintained for the total spectrum of patients seen in tertiary care centers; therefore, it is part of a larger health care system extending beyond its walls for these transferred patients. These patients' outcomes are, in part, due to the care they received and the appropriate decision to transfer. Second, we did not wish to gain any advantage by either excluding or counting as survivors these transferred patients.

TABLE 1.—*Predicted and Actual Mortality* in 681 Patients in a Pediatric Intensive Care Unit*

Mortality Category, %	Survivors		Nonsurvivors	
	Observed, No.	Predicted, No.	Observed, No.	Predicted, No.
0-5	592	588.2	4	7.8
5-30	55	52.2	4	6.8
>30	11	8.0	15	18.0
Totals	658	648.4	23	32.6

*χ^2 (3 *df*) = 4.85, *P*>.2.

Results

We included 681 patients for 1989 to 1990 in the analysis. There were 320 patients younger than 2 years, 250 between 2 and 10 years, and 111 older than 10 years. Diagnoses were about evenly divided among infectious diseases, traumas, and other illnesses. There were 23 deaths (3.4%). Causes of death included vehicular trauma (7 patients), sudden infant death syndrome (4), drowning (1), congenital heart disease with complications such as sepsis (3), chronic lung disease with complications (2), airway obstructions after cardiopulmonary arrest in referring hospitals (2), head trauma (1), brain tumor (1), central hypoventilation syndrome (1), and cardiopulmonary arrest of unknown cause (1). The PRISM score predicted 32.6 deaths (Table 1; $\chi^2[3\ df] = 4.85$, $P > .2$). The distribution of outcomes in Table 1 indicates close agreement in the highest risk group (15 deaths observed, 18 predicted) and the moderate risk group (4 deaths observed, 6.8 predicted). The largest discrepancy occurred in the lowest risk group in which 4 deaths were observed but 7.8 were predicted.

To ensure an unbiased interpretation of the information, three modified scenarios were evaluated. First, because the lowest risk group might have included patients who would have been admitted to intermediate care units at other hospitals, this risk group was eliminated. There were 19 deaths observed and 24.8 predicted in this truncated sample ($\chi^2[2\ df] = 2.96$, $P > .25$). Second, one transferred patient with the acute respiratory distress syndrome was deteriorating at the time of transfer but eventually survived and was counted as a survivor. If this patient had been counted as a nonsurvivor, with the lowest risk group eliminated, there would have been 20 deaths observed with 24.8 predicted (χ^2 [2 *df*] = 2.20, $P > .25$). Third, completely eliminating the transferred patients from the analysis, as well as from the lowest risk group, would result in 19 deaths observed and 24.2 predicted ($\chi^2[2\ df] = 2.53$, $P > .25$).

Discussion

The rigorous multi-institutional evolution and validation of PRISM make it suitable for outcome-based quantitative quality assurance studies in single PICUs.[3] Before PRISM scores were available, performance evaluations of intensive care units using crude mortality rates were extremely difficult because severity of illness and diagnostic distributions varied. With the widespread availability of computer technology and appropriate software, the same rigorous validation methods can be readily used in single PICUs or regions to investigate quality issues of local or national interest. The results of the multi-institutional studies of PRISM indicate there is a consistent relationship between the physiology-based predictors and the outcome (mortality risk). The constancy of this relationship as demonstrated in the multicentered trials is the backbone of the use of these predictors for quality assurance purposes. If the observed number and distribution of outcomes are similar to the predicted number and distribution of outcomes, then the performance of the institution is equivalent to those institutions validating the predictor in the multicentered trial. If the performance of the institution differs from that expected, an explanation must be sought.

As with any test, physicians using this quality assurance method will need to understand its strengths and limitations, such as when false-positive and false-negative results can occur and peculiarities of the method. This method is not designed to replace other quality assurance tasks such as evaluations of nosocomial infections and spontaneous extubations. It will, however, provide a more objective and rigorous review than mortality conferences.

Several studies show that this method of quality assurance, the comparison of observed and predicted numbers of outcomes, can be successful. In Oregon the records of all children who received critical care for trauma and respiratory failure for six months were evaluated.[7] Evaluating the observed and predicted death rates showed that the care of children in adult intensive care units was associated with a

mortality almost 40% higher than expected, whereas PICU care had accurately predicted death rates. Another pediatric study of a single institution showed that the mortality by severity of illness improved after an intensive care specialist joined the staff.[8] Knaus and associates, in evaluating 13 adult intensive care units in medical centers, found that the actual mortality was well predicted by the APACHE II scores in 11 of the 13 hospitals[9]; in 2 hospitals, however, APACHE II did not accurately predict mortality rates. In an a posteriori analysis, the investigators were able to relate their findings to the organizational structure of care delivery in the intensive care units. They concluded that the degree of the coordination of care may significantly affect the outcome.[9] This method is analogous to using the Trauma Score and Injury Severity Score to evaluate results from trauma.[10,11] The usefulness of objective analyses for trauma quality assurance methods is also evident. Shackford and colleagues compared the outcomes, controlling for severity of illness, before and after the regionalization of adult trauma care.[12] After the regionalized trauma system was instituted, adult outcomes controlled for severity of illness were improved.

The current study is consistent with the conclusion that the quality of care in this community hospital PICU as measured by PRISM is comparable to that of tertiary care centers. The observed number of deaths was similar to the number predicted by the PRISM method. Because the use of PRISM in community PICUs has not been tested previously, we varied the criteria for including patients without changing the statistical conclusions. In all cases the observed and predicted number of outcomes corresponded.

Guidelines commonly address the areas of personnel and equipment.[13] Equipment in this PICU, such as monitors and ventilators, was similar to that in other PICUs. The nurses had degrees and training equivalent to those in other hospitals; the pediatric intensive care training was done in house. As occasionally occurs in other hospitals, respiratory therapists had varying pediatric backgrounds and often had responsibilities that included patients outside the PICU. Several major differences between the PICU at this hospital and those of tertiary centers were present. There were no in-hospital pediatricians or house staff who were responsible for the patients 24 hours a day. Because the maximum physician response time was 20 minutes, nurses were trained to handle emergencies. In addition, because consultations were unavailable in certain subspecialties, such as pediatric hematology-oncology and pediatric neurosurgery, patients with certain diagnoses had to be transferred. Those few patients were transferred as soon as they were stable. The PICU was thus able to focus on patients who it was best equipped to manage.

More research is needed to evaluate whether physiology-based predictors are applicable to nontertiary hospitals. This analysis illustrates several unresolved issues. There is a need for a consistent method of determining which patient transfers should be included as survivors, which as nonsurvivors, and which should be eliminated. Obviously, if patients who were about to die were transferred and then counted as survivors, the resulting analysis would indicate a better level of care than actually existed. The data indicate there may need to be better methods to account for possible selection and lead-time bias.[14,15] Although not statistically significant, PRISM scores seemed to underpredict the number of deaths. This could result from different types of patients being admitted to this PICU compared with the patients admitted to the PICUs creating and validating the PRISM score. For example, all patients have a measurable mortality risk, but those admitted from the emergency department with physiologic instability responsive to therapy are at less risk than those admitted from other PICUs where extensive attempts have already been made to correct the problem.

Conclusion

Pediatric intensive care units may be self-designated or designated by an authorized body using objective criteria. Because pediatric intensive care in some localities must be provided in community hospitals, quality assurance methods applicable to community as well as tertiary hospitals are desirable. Regardless of the a priori designation, quality assurance techniques must be applied to outcomes to confirm an acceptable level of care on an ongoing basis. The study reported herein indicates that, based on the PRISM method of analysis, tertiary level quality of care for selected patients is possible in a community hospital.

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Articles

Screening Mammography Reports
Toward Clear, Concise Clinical Descriptions

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The American College of Radiology (ACR) has led the way in certifying the quality of mammography units in the United States. Beginning in 1987, the ACR, using detailed technical evaluation including actual mammography film evaluation, has accredited more than 5,000 of the estimated 11,000 mammography units in operation in the United States. In addition, continuing medical education in mammography has been given by the ACR to more than 11,000 of the estimated 31,000 radiologists practicing in this country. This is notable progress toward ensuring the availability of quality screening mammography. These quality-assurance programs by the ACR are continuing to reach even larger numbers of mammography units and the radiologists who interpret the mammograms.

Until now, however, the mammography report—the crucial communication link between the clinicians and the radiologists—was left to the devices of the radiologists dictating the report. Particularly with screening mammography, lengthy, ambiguous reports without a clear clinical conclusion and recommendation confused and often frustrated clinicians ordering the mammograms and created problems in patient management. The ACR's *Breast Imaging Reporting and Database System* should eliminate this confusion and frustration for both clinicians and radiologists.

Responding to the recognized need and a barrier to the widespread use of screening mammography, the ACR formed a panel of nationally recognized expert mammographers and sought input from primary care providers for women, other physicians, interested government and nongovernment institutions and organizations, and women themselves. The penultimate ACR document was presented and freely discussed at a workshop, partially supported by the Centers for Disease Control, the National Cancer Institute, and the US Food and Drug Administration, on November 7 and 8, 1991, in Washington, DC. The final document should be widely distributed soon.

Breast Imaging Reporting and Database System provides a standardized lexicon and format for concise, clear mammography reports. The recommended report organization is as follows:

- A succinct description of the overall breast composition;
- Significant findings and modifiers;
- Size of the significant lesion;
- Associated findings;
- Clinical location;
- Overall assessment;
- Future action.

The recommended final assessments are as follows:

- No evidence of malignancy;
- Benign findings;
- Probably benign finding—short interval follow-up;
- Suspicious abnormality for which a biopsy should be considered;
- High probability of breast cancer.

Using the approved, precise terminology, the mammography reports should describe the breast composition (density), masses (measured size, shape, margins, density, and location), calcifications (type, morphology, probable cause, distribution, and location), and any associated findings.

Using this protocol and lexicon, a sample mammography report for screening might be,

> The present examination is compared to previous mammograms: the breast is all fat; no masses, significant calcifications, or other findings are seen.
> *Assessment:* There is no mammographic evidence of malignancy.

and for a patient with a mammographically detected mass,

> The breast is almost entirely fat. There is a 7-mm irregular spiculated mass in the anterior 11 o'clock region of the right breast. No other abnormalities are identified.
> *Assessment:* There is a malignant-appearing lesion in the right breast.

It is further stated, "The radiologist may wish to include a recommendation for the interval until the next routine study." Most clinicians would welcome this follow-up recommendation.

The ACR data-base system contains an extensive coding system for the clinical information, mammography report, and histologic diagnosis that can form a standardized, computer data base. This would permit the rapid, accurate interchange and meaningful analysis of the mammographic data. The clinical research potential is exciting and could respond to the multitude of currently unanswered questions about screening and diagnostic mammography.

In the future, the ACR Breast Imaging Committee will evaluate producing the *Breast Imaging Reporting and Database System* computer software for use in physicians' offices. This should greatly facilitate accurate record keeping and consistent follow-up. Another issue is the information that goes directly to the patient. Because an increasing number of women now request screening mammography directly, a report in lay language with minimal potential for misinterpretation should go to the patient. Some primary care providers prefer to have their patients who have screening mammograms that do not reveal any significant abnormality receive a report directly from the radiologist with a copy to the physi-

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cian's office for filing in the patient's medical record. Many mammography centers routinely send "well letters" to patients when no abnormality is noted. Should the patient receive an exact copy of the entire mammography report or a modification in lay terms? This and similar questions are currently being explored by the ACR Breast Imaging Committee.

All of this is good news to professionals providing health care to women and to all women having screening mammography. Educating professionals and laypersons with clear, concise communication is essential to the success of the goal that all women in the United States older than 35 years have initial screening mammography and continue to have annual screening mammograms after age 40.

* * *

DOWAGER'S HUMP

From the balcony
  I watch the choir proceed
up the aisle like two lines
  of twisted trees,
silver tops sway
  from side to side,
as each step uproots them,
  wobbles them towards the risers.

They fear falling, these women,
  fear the cause of a fall,
bone snapping in midair
  to rearrange their years.

I see several with dowager's hump;
  anyone could be my mother
with a twisted "S" for a spine
  hidden under her clothes,

and I want to run home, swallow
  calcium, walk, stretch,
do whatever can be done, today,
  to avoid their paralyzing posture.

Mother said it was rickets,
  her childhood disease, or
was it the lack of fruit?
  lack of milk?
when no one knew about vitamins,
  and no one ever said
you're part of the universe,
  made of the same stuff,
iron and zinc and calcium
  and when something's missing
the rock crumbles,
  trees tumble,
stars disappear,
  or one hip shifts out of line,
shoulders pitch forward
  and mother cries
before the dressing room mirror.

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Conferences and Reviews

Erythropoietin Therapy in Patients With Chronic Renal Failure

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Symptomatic anemia is a common complication of chronic renal failure. Treatment is now possible with the availability of recombinant human erythropoietin (epoetin alfa). Previous experimental studies have suggested that correcting the anemia of chronic renal failure may be harmful in that renal failure may be accelerated. Although experience with this drug has been primarily restricted to its use in patients with end-stage renal disease, several recent trials have been reported in patients with varying degrees of chronic renal failure. We review these studies with particular reference to the progression of renal failure and the drug's reported side effects. We conclude that the use of epoetin is beneficial and well tolerated and that there is no compelling evidence for the acceleration of renal failure associated with its use in patients.

(Pinevich AJ, Petersen J: Erythropoietin therapy in patients with chronic renal failure. West J Med 1992 Aug; 157:154-157)

Recombinant human erythropoietin (epoetin alfa [r-HuEPO]) was approved in 1989 for use in treating the anemia of chronic renal failure. This drug is now in widespread use and has been shown to be efficacious and safe in patients with end-stage renal disease, provided that monitoring guidelines are followed.[1-3] Objective measures such as transfusion requirements,[3] exercise capacity,[4] quality of life,[4] and cognitive[5] and myocardial function[6,7] are often improved by the use of epoetin. Costs of this therapy are substantial, however, averaging about $6,000 per patient annually.[8] Patients with the anemia of chronic renal insufficiency not yet requiring dialysis constitute a subgroup that has received considerably less attention in experimental trials. We will summarize the use of epoetin in these patients and the evidence for the benefits and risks associated with its use.*

Anemia of Chronic Renal Failure

The anemia of chronic renal failure is multifactorial. The major factor is a relative deficiency of erythropoietin synthesis by the failing kidneys.[9] Although serum erythropoietin levels are often in the "normal" range, they are inappropriately low for the degree of anemia exhibited. Other factors possibly causing the anemia, particularly in patients with end-stage renal disease, include decreased red cell survival, iron deficiency, aluminum toxicity, osteitis fibrosa cystica, folate deficiency, uremic inhibitors of marrow function, and blood loss in the extracorporeal circuit.[9] The anemia usually begins at a serum creatinine level of about 177 μmol per liter (2 mg per dl) or a glomerular filtration rate of about 0.05 liters per minute. It is characteristically normocytic and normochromic and is associated with a subnormal reticulocyte response. The severity of the anemia differs among disease types and among individual patients having the same disease. For example, patients with interstitial disease causing renal insufficiency have a greater degree of anemia than do patients with glomerular disease, whereas patients with polycystic kidney disease have a milder or no anemia.[10]

It would seem logical that epoetin therapy in a predialysis patient should not differ substantially from its use in a patient with end-stage renal disease. Details of epoetin therapeutic guidelines and side effects have been published in a number of reviews[11-14] derived mainly from data obtained from patients already on dialysis. The major problems associated with the use of epoetin in patients with end-stage renal disease include worsening of their condition or the development of hypertension, hyperkalemia, iron deficiency, and perhaps an increased incidence of thrombotic events and seizures. The frequency of these treatment-related complications in predialysis patients is under investigation, as is the question of whether predialysis epoetin therapy can accelerate the progression of kidney failure to end-stage renal disease. This last issue has been a subject of intense discussion recently in nephrology circles and will be reviewed herein along with other aspects of epoetin therapy.

Assessing the Degree of Renal Failure

Myers and co-workers were the first to report the effect of acute changes in the hematocrit on kidney function in rats.[15] The single-nephron glomerular filtration rate (GFR) along with renal plasma flow and the other determinants of glomerular filtration were measured by micropuncture. The results are summarized in Table 1. As the hematocrit increased to polycythemic levels (0.63 [63%]), the single-nephron GFR fell significantly. This was due to a fall in the single-nephron renal plasma flow because the associated rise in the transcapillary hydraulic pressure would increase, not decrease, glomerular filtration. The creation of anemia to a hematocrit of 0.23 (23%) was associated with opposite effects—that is, an increase in single-nephron GFR and renal plasma flow and a fall in the transcapillary hydraulic pressure.

Garcia and associates, in a more relevant study, examined the effects of the long-term administration of epoetin in a

*See also "Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia" by A. J. Erslev, MD, on pages 195-196 of this issue.

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TABLE 1.—*The Effects of Acute Changes of Hematocrit in Normal Rats**

Physiologic Variable	Rats			
	Control	Anemic	Control	Polycythemic
Hematocrit	0.51	0.21†	0.51	0.63†
ΔP, mm of mercury	33	30†	38	45†
Single-nephron glomerular filtration rate, nl/min	30	40†	32	24†
Single-nephron renal plasma flow, nl/min	81	156†	88	49†

ΔP = transmembrane hydraulic pressure difference across the glomerular capillary

*From Myers et al.[15] †$P<.05$ versus control.

TABLE 2.—*The Effects of Epoetin in Rats With a 5/6 Nephrectomy**

Physiologic Variable	Rats		
	Anemic	5/6 Nephrectomy	Epoetin Given
Hematocrit	0.27	0.42†	0.50‡
Mean arterial pressure, mm of mercury	123	143†	166‡
ΔP, mm of mercury	34	48†	58‡
Single-nephron glomerular filtration rate, nl/min	88	80	50‡
Urine protein, grams/day	0.004	0.015†	0.05‡
Glomerular sclerosis, %	5.6	12.8†	33.2‡

ΔP = transmembrane hydraulic pressure difference across the glomerular capillary

*From Garcia et al.[16] †$P<.05$ versus anemic and epoetin-treated rats. ‡$P<.05$ versus anemic and nephrectomized rats.

renal ablation model of chronic renal failure.[16] In untreated control rats, mild anemia, hypertension, progressive proteinuria, and structural renal damage developed. The results are summarized in Table 2. Relative polycythemia developed in the epoetin-treated group. Similar to the previous study, a fall in the single-nephron GFR and an increase in the transcapillary hydraulic pressure were found. Furthermore, this was associated with increased proteinuria and structural damage to the kidney. In the polycythemic group, 33.2% of glomeruli were sclerosed, compared with only 12.8% in the mildly anemic controls. Interestingly, when the controls were made more anemic, only 5.6% of the glomeruli were sclerosed. Both studies found an elevated transcapillary hydraulic pressure, which is hypothesized to be a major factor for progression in other models of chronic renal failure.[17] The authors concluded, based on their own observations and those of Myers and colleagues, that "anemia is in fact a hemodynamically favorable adaptation to chronic renal disease, and its overly vigorous correction may have adverse renal hemodynamic and structural consequences."[16(p6142)] This conclusion is consistent with previous findings that some polycythemic patients—those with cyanotic heart disease or cor pulmonale—exhibit glomerular proteinuria that is reversible with phlebotomy,[18] and in some cases structural derangements such as glomerular congestion and sclerosis develop.[19]

Epoetin Therapy and Kidney Failure

Several studies have reported the effect of the use of epoetin in patients with progressive kidney failure (Table 3).[20-33] Most investigators used conventional epoetin dosing and monitoring guidelines with hematocrit targets in the range of 0.33 to 0.39. Administering epoetin was successful in raising the hematocrit in virtually all patients. The severity of renal impairment on entry to the study varied among the

TABLE 3.—*The Use of Recombinant Human Erythropoietin (Epoetin) in Predialysis Patients*

Study	Patients on Epoetin Therapy, No.	Controls	Duration of Treatment	Findings
Brown and Friedman, 1990[20]	8	Self	1 yr	No significant (NS) change in serum creatinine level
Hori et al, 1989[21]	7	Self	4 wk	NS change in reciprocal of serum creatinine (1/cr) slope
Lim et al, 1989[22]; Lim et al, 1989[23]	10	Self	11-29 mo	NS change in 1/cr slope and serum creatinine level
Onoyama et al, 1989[24]	7	Self	4 wk	NS change in inulin clearance
Kleinman et al, 1989[25]	7	Placebo	12 wk	NS change in 1/cr slope
Abraham et al, 1990[26]	8	Placebo	37 wk	NS change in 1/cr slope and inulin clearance
Frencken et al, 1989[27]	24	Self	8 mo	NS change in 1/cr slope
Eschbach et al, 1989[28]	17	Self	1 yr	NS change in 1/cr slope
Brown and Friedman, 1989[29]	5	Self	1 yr	NS change in serum creatinine level
Schwartz et al, 1990[30]	8	Self	1 yr	Creatinine clearance decreased 0.013 to <0.005 liters/min
Traindl et al, 1990[31]	19	Self	5-20 wk	NS change in serum creatinine level
Frencken et al, 1990[32]	8	Self	8 wk	Inulin clearance fell from 0.0082 to 0.0074 liters/min
USRHEPSG, 1991[33]	86	Placebo	8 wk	NS change in 1/cr slope and creatinine clearance
		Self	1 yr	NS change in 1/cr slope and creatinine clearance
Total	214		1-29 mo	

USRHEPSG = US Recombinant Human Erythropoietin Predialysis Study Group

series, with the majority having baseline serum creatinine values above 265 μmol per liter (3 mg per dl). Most studies using the slope of the reciprocal of serum creatinine level versus time detected no change in the rate of progression of kidney failure before and after treatment.[34] Studies in which the decline in renal function was measured more rigorously with inulin clearances also confirmed these observations.[24,26] Furthermore, the few patients who did progress to worsened renal insufficiency or end-stage renal disease did not do so at an accelerated rate during treatment when compared with their pretreatment period. Follow-up ranged from 1 to 29 months, a time frame that is representative of the duration between the onset of severe anemia and the progression to end-stage disease.

Several explanations have been proposed for the discrepancy between the experimental findings in the two animal studies and those in patients with chronic renal failure, including that the sample size was too small, the follow-up time was too short, and insensitive means were used to monitor progression.[35,36] The most likely explanation is that these rodent models are not completely analogous to the clinical situation. In particular, Myers and co-workers studied the acute effect of an increased hematocrit to polycythemic levels, hardly a therapeutic goal in patients with chronic renal failure.[15] Moreover, Garcia and colleagues used rats with uncontrolled hypertension and a relative polycythemia in the treatment group.[16] The hypertension may have contributed independently to the progression of renal failure, and the level of hematocrit correction is much higher than that targeted in any of the patient studies. The weight of evidence thus far in humans, therefore, does not support the concerns extrapolated from these studies of animals.

Other variables besides the progression of renal failure have been evaluated in patients. Studies of the development or worsening of hypertension in predialysis patients receiving epoetin have been inconclusive, with results varying widely. In the largest study, no statistically significant change in systolic or diastolic blood pressure was noted in epoetin-treated subjects.[33] The authors did, however, note a trend toward an increased prevalence of hypertensive events in patients whose hematocrits increased at rates greater than 0.002 per day. No study has found a definitive association between predialysis epoetin use and an increased incidence of hyperkalemia, thrombosis, or seizures. Patients treated with epoetin before the development of end-stage renal disease exhibit improved quality-of-life scores similar to their counterparts who are in the end stages of disease.[25] The use of epoetin may in fact improve the quality of life to such an extent that the decision to initiate dialysis may be made more difficult as some "uremic" symptoms such as lack of energy may in fact be due to the anemia. Symptoms such as anorexia and nocturnal leg cramps, however, were shown to often persist despite the correction of anemia.[25]

Dosage and Monitoring of Erythropoietin Therapy

Strict guidelines have been established for epoetin dosing for patients with end-stage renal disease[13]; dosage recommendations do not differ for predialysis patients. The usual starting dose is 50 to 100 units per kg of body weight per injection, administered three times a week either intravenously or subcutaneously. Predialysis patients can administer epoetin to themselves provided they have demonstrated their ability in this regard. In predialysis patients who may not need frequent medical visits, a starting dose of 100 units per kg per week can be administered on a once-per-week basis. Dosage should be reduced when the hematocrit reaches the target range of 0.30 to 0.33 or increases by more than 0.04 in any two-week period. Dose changes should generally be in the range of 25 units per kg when using a three-times-a-week schedule. If the hematocrit exceeds 0.36, epoetin therapy should be withheld until the hematocrit is 0.33 or less, and then the dose should be reduced. The median epoetin maintenance dose is about 75 units per kg three times a week but may range from 12.5 to 525 units per kg three times a week. Average maintenance dosage requirements appear to be somewhat less for subcutaneous than for intravenous administration, perhaps because the subcutaneous route provides a longer exposure of the hormone to erythroblast progenitors.[23]

Monitoring of epoetin therapy is essential.[13] Before and during therapy, transferrin saturation must be at least 0.20 (20%) and the serum ferritin level should be at least 100 μg per liter (100 ng per ml). Supplemental iron is usually required to maintain these levels. The hematocrit should be determined twice per week until it has stabilized in the target range and the maintenance dose has been established. After any dose adjustment, the hematocrit should also be determined twice a week for at least two to six weeks. It should be checked at regular intervals thereafter. Renal function and electrolyte status as well as blood pressure must also be regularly assessed. In evaluating an apparently poor response to epoetin therapy, many causes may require consideration, including iron deficiency, occult blood loss, aluminum intoxication, vitamin deficiencies, osteitis fibrosa cystica, hemolysis, or underlying infectious, inflammatory, malignant, or hematologic processes.

Conclusion

The anemia of chronic renal failure in predialysis patients can be successfully corrected with epoetin therapy using management guidelines developed for patients with end-stage renal disease. Its use in predialysis patients may be associated with similar side effects. The quality of life is improved as anemia is corrected in patients before the progression to end-stage disease, similar to that in patients with irreversible renal failure. An important note is that correcting anemia does not appear to accelerate the progression of renal insufficiency in humans. We recommend that anemic predialysis patients be cautiously prescribed epoetin therapy, provided that therapeutic and monitoring guidelines are followed.

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The Second Century of the Antibody
Molecular Perspectives in Regulation, Pathophysiology, and Therapeutic Applications

Moderator
JONATHAN BRAUN, MD, PhD

Discussants
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This is an edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles, California. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

The modern age of immunology began in 1890 with the discovery of antibodies as a major component of protective immunity. The 2nd century of the antibody begins with a focus on the molecular physiology and pathophysiology of immunoglobulin production. Numerous human variable-region antibody genes have been identified through advances in molecular cloning and anti-variable-region monoclonal antibodies. Some of these variable-region genes are now known to be involved in specific stages of B-lymphocyte differentiation and immune development. This connection has yielded new insights into the pathogenesis of immune dyscrasias and lymphoid neoplasia; common variable immunodeficiency and cryoglobulinemia are highlighted here. The molecular regulation of immunoglobulin expression suggests new targets for pathogenesis and clinical intervention. Finally, genetically engineered antibodies offer novel opportunities for diagnostic and therapeutic applications.

(Braun J, Saxon A, Wall R, Morrison SL: The second century of the antibody—Molecular perspectives in regulation, pathophysiology, and therapeutic applications. West J Med 1992 Aug; 157:158-168)

JONATHAN BRAUN, MD, PhD*: One hundred years ago, it was well known that a resistance to infections could be elicited by specific immunity. The mechanism of this immunity was unknown, however. During the decade of the 1880s, Loeffler, Roux, and Yersin showed that the diseases diphtheria and tetanus were caused by exotoxins. These diseases were at the time leading causes of death in children, and the findings set off intense efforts by members of Robert Koch's laboratory to find out how immunity to these toxins occurred.

In 1890, two laboratory researchers, Emil Behring and Shidasabura Kitasato, together discovered that the immunity was due to a cell-free serum component that was specific to the toxin used for immunization and that, when injected into a nonimmune recipient, neutralized the toxin's lethality. These findings were reported in the December 1890 issue of *Deutsche Medizinische Wochenschrift*[1] and electrified the world's scientific community. A year later on Christmas night, Behring used this strategy of passive immunization with antitoxin serum to treat a child with diphtheria.

In this conference, we shall emphasize current research focusing on the molecular and developmental regulation of antibodies and its relation to issues in immune pathogenesis and therapeutics.

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Variable-Region Genes

Variable-Region Genes in B-Cell Development

The capacity of persons to produce an almost limitless range of antibody specificities is a key feature of humoral immunity. Its molecular basis was a mystery until 1977 when Tonegawa and colleagues recognized that each active antibody gene was assembled from several gene segment families (V, D, J, and C) by a novel DNA rearrangement process.[2] Diversity is created from the large number of family members (in the case of the V gene family, 100 or more), independent assortment and combination of segments, and imperfect segment joining. All told, these factors permit the generation of more than 10^8 antibody species.[2]

An important practical result of this work was the introduction of recombinant probes for antibody use, which provide an unambiguous identification of B-lymphocyte clones and direct characterization of their genetic relatedness. An early insight from such analysis occurred in studies of B-cell development. It is well known that antibody diversity dramatically increases during fetal development and its cellular counterpart in the pre-B-cell stage. The work of Malynn and associates, however, showed that this increase is not merely quantitative but involves changing patterns of V-gene usage.[3] At the earliest stages, only a few V genes are accessible for rearrangement into active antibody genes. The resulting fetal

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ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
CVI = common variable immunodeficiency
HIV = human immunodeficiency syndrome
IFN-γ = interferon gamma
Ig = immunoglobulin
IL = interleukin
LPS = lipopolysaccharides
PMA = 12-*O*-tetradecanoylphorbol 13-acetate
TGF-β = transforming growth factor β

antibody repertoire thus contains predominantly these unusual antibodies whose specificity and function, although apparently important for immune ontogeny, remain a mystery. The V_H5 and V_H6 gene families are the earliest detected in human fetal development,[4] followed by certain members of the V_H1 and V_H3.[5,6] Some of these V_H genes are notable for their predominance in certain categories of B-cell neoplasia (Table 1). With maturation a much fuller range of V genes is used, so that the abundance of V genes in the mature B-cell population is roughly proportional to their representation in the immunoglobulin loci.[3] An important role is played by T lymphocytes in this developmental switch in V-gene use, possibly through conventional immune selection.[3,7] In this regard, there is much interest in establishing whether such selection involves exogenous versus "self" antigens, which might bear on the genesis of certain classes of autoantibodies.

A second major expansion and diversification of the antibody repertoire occurs during childhood.[8,9] Recent work in our laboratory has shown that the abundance of B cells in lymphoid germinal centers—representing a precursor stage in the development of immunologic memory—is increased in young children (2 to 4 years) but adjusts to adult levels by preadolescence (8 to 14 years).[10] This evolving abundance is associated with a qualitative shift in the clonal pattern of B cells; for example, the use of certain V_H1 genes is delayed until preadolescence. It may be notable that this corresponds to a shift in serum immunoglobulin (Ig) A and a response to *Haemophilus influenzae* infection to adult levels.[8,11] Other V genes are significantly used only by B cells in the blood and lymphoid mantle zones, most likely representing the mature memory population. These V genes, including V_H3_L (a subgroup of the V_H3 family) and humVκ328 (a member of the VκIIIb light-chain family), can thus be used as clonal markers for this stage of B-cell maturation (Figure 1[10]; and J. Braun, MD, PhD, and Y. Valles-Ayoub, MD, PhD, unpublished data, September 1991).

The V_H3_L marker has been informative regarding the pathogenesis of two immunodeficiency diseases. Common variable immunodeficiency (CVI) has been related by various in vitro assays to an intrinsic block in the B cell differentiative potential (discussed later). A collaborative study with Andrew Saxon, MD, showed that patients with this disease are typically deficient in V_H3_L B cells, a finding consistent with their deficit in mature blood or mantle zone cells.[12]

In a separate study of the human immunodeficiency virus (HIV), infection was prompted by the early occurrence of paradoxic B-cell hyperplasia and humoral immune deficiency. Humoral immune deficiency is seen as a poor response to polysaccharides in vivo,[13] pokeweed mitogen in vitro,[14] a peculiar "bare follicle" histologic appearance of lymph node,[15] and a decline in Leu-8 B-cell expression.[16] We noted that all these features could be attributed to a deficit in the mantle zone B-cell subpopulation. In a study of 20 HIV-positive persons, a selective and profound deficit of V_H3_L B

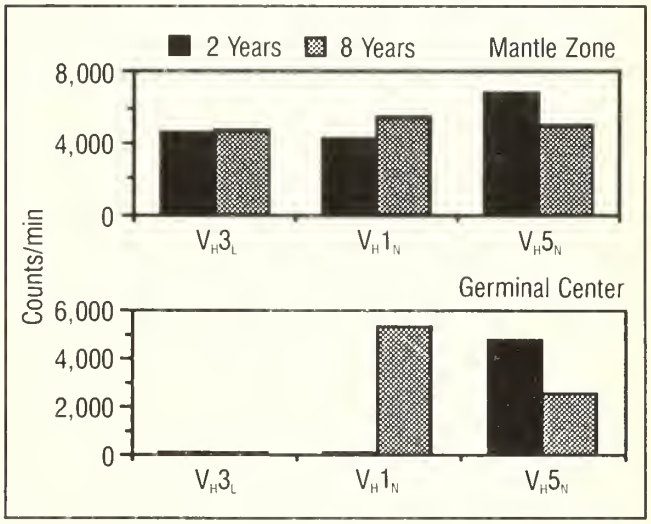

Figure 1.—The effect of age and developmental subpopulation (mantle zone versus germinal center) is shown on the abundance of B cells bearing V gene subfamilies. The representation of V_H1_N and V_H3_L is restricted by these measures to the mantle zone (mature-memory) stage; V_H5_N exemplifies an unrestricted V gene subfamily (from Valles-Ayoub et al[10]; adapted with permission from *Blood*).

TABLE 1.—*Distinct Development or Pathophysiology of B Cells Using Certain V Genes*

Gene	*Description*	*Abundance, %*	*Reference*
Vκ325 . .	CLL	25	Kipps et al, 1990[17]; Kipps et al, 1988[20]
	Waldenström's macroglobulinemia	33	Kipps et al, 1990[17]; Kipps et al, 1988[20]
	Mixed cryoglobulinemia	35	Kipps et al, 1990[17]; Kipps et al, 1988[20]
	Sjögren's syndrome	~15	Kipps et al, 1989[22]
V_H51P1. .	Fetal	--	Schroeder et al, 1987[5]
	CLL	20	Kipps et al, 1989[19]
	Well-differentiated non-Hodgkin's lymphoma	10	Kipps et al, 1989[19]
V_H5.	Earliest fetal	--	Cuisinier et al, 1989[4]
	CLL	20	Humphries et al, 1988[18]
V_H6.	Earliest fetal	--	Cuisinier et al, 1989[4]
	Most proximal	--	Mayer et al, 1990[21]
	Anti-DNA	--	Mayer et al, 1990[21]

CLL = chronic lymphocytic leukemia

cells was found.[17] These findings suggest that the B-cell immune dysfunctions in these two diseases may involve a developmental block at the germinal center stage. In the case of CVI, the block is probably intrinsic, whereas in HIV infection it presumably reflects a deficit in the $CD4^+$ T-cell role needed for the transition of B cells from the germinal center to quiescent memory cell stage. This point is further discussed in the section by Saxon.

B-Cell Neoplasia and Autoimmunity

Like normal lymphocytes, malignant B cells typically express or secrete a clonal antibody. A combination of molecular cloning and monoclonal antibody techniques has shown that B cells bearing certain antibodies are disproportionately represented in lymphoid malignant neoplasia (Table 1). Studies by Miller and co-workers of follicular non-Hodgkin's lymphomas have shown that at least a third of 150 independent lymphomas can be grouped into recurrent clonal families detected by shared idiotypes (unique antigenic determinants on the clonal antibody).[18] In the narrower group of $CD5^+$ B-cell malignancy—chronic lymphocytic leukemia, small cell lymphocytic lymphoma—Kipps and colleagues found that about 50% of cases may be grouped by a panel of five anti-idiotypic probes.[19] Accordingly, a disproportionate occurrence of certain light- and heavy-chain V genes in these malignant disorders has been reported by several groups.[20-23]

What is the basis for the malignant predilection of these B-cell clones? One is the fetal development process: Some of these V genes are notable for their predominance early in ontogeny, suggesting that the biologic mechanism underlying selective V-gene use in development may be directly relevant to lymphomagenesis. Another is autoimmune pathophysiology: Although lymphocytes bearing these V genes in normal B-cell populations are rare, they are notable for their predominance in mixed cryoglobulinemia and autoimmune tissue infiltrates associated with Sjögren's syndrome.[21,22,24] This may indicate common pathogenetic mechanisms shared by this autoimmune disease and certain categories of B-cell neoplasia.[23] In view of the novel and promising use of anti-idiotypic monoclonal antibodies for the treatment of B-cell lymphomas, it is conceivable that anti-idiotypic therapy may also be useful in autoimmune diseases for which a restricted clonal population of pathogenetic B or T lymphocytes are involved.

Common Variable Immunodeficiency—A Maturational Arrest in Germinal Center B-Cell Development

Andrew Saxon, MD*: Common variable immunodeficiency is a syndrome wherein various pathophysiologic states lead to the inability to produce both normal quantitative and qualitative antibody responses.[25,26] Although it may occur in infancy, it generally is noted at puberty or later, and in most patients there is no evidence for dominant or recessive inheritance.[27] Common variable immunodeficiency has represented the expression of several acquired defects in humoral immunity. Our analysis of the phenotypic, functional, and molecular aspects of the B cells from patients with the disorder, however, suggests that in most patients it may represent a relatively uniform defect in B-cell development.

The hallmark of CVI is the presence of hypogammaglobulinemia that generally affects all the major immunoglobulin effector isotypes—IgM, IgG, and IgA—involved in protecting from infection. Not surprisingly, patients almost uniformly present with complaints of bacterial infection, generally of the respiratory system (sinusitis, bronchitis, or pneumonia).[28] As in other immunodeficiency states, the characteristics of the infections in these immunocompromised patients are their increased frequency, increased severity, the failure to resolve with appropriate therapy, and the presence of unusual organisms. Common variable immunodeficiency manifests two other features that are less obviously related to the humoral immunodeficiency: lymphoid hyperplasia, particularly of the gastrointestinal tract, with an increased frequency of lymphoproliferative disorders,[29,30] and the occurrence of various autoimmune phenomena, including rheumatoid-like arthritis, idiopathic thrombocytopenia, atrophic gastritis with pernicious anemia, secretory diarrhea, parotitis, Guillain-Barré syndrome, and sicca complex.[31-33]

B cells (defined as cells bearing membrane Ig) are present in normal numbers in the circulation and the tissues of two thirds of patients with the disorder and in reduced numbers in the remaining third.[27] This is in contrast to X-linked agammaglobulinemia, which involves an essentially complete deficit in membrane Ig-bearing B cells due to a developmental block at the pre–B-cell stage. Instead, the problem in CVI is the failure of these B cells to mature into Ig-secreting cells in vivo. In most patients, this is reflected in vitro by the inability of their B cells to secrete Ig even when provided with appropriate stimuli for terminal differentiation.[34-36] Although diverse immune mechanisms have been proposed as the underlying cause of this deficit, it is this failure to develop high-rate Ig-secreting cells that directly accounts for the profound deficiency of serum immunoglobulins and resultant recurrent bacterial infections.[28]

Functional and Molecular Features of Common Variable Immunodeficiency

Resting B cells must pass through the stages of activation, proliferation, and then differentiation to become high-rate Ig-secreting cells.[37,38] Thus, resting B cells need an initial activation step, after which they enter the G1 phase of the cell cycle, increasing their expression of DR antigens and displaying receptors for proliferative signals—that is, B-cell growth factors such as interleukin (IL) 4. In the presence of these growth factors, the activated B cells can undergo several rounds of cell division. Finally, under distinctive differentiation drives, the B cells enter a maturational phase in which immunoglobulin is synthesized and secreted. These stages of development can be analyzed in vitro by assaying the response to defined activation, proliferation, and differentiation signals.[37-39]

B cells from 15 patients with CVI were analyzed with respect to this in vitro developmental pathway to determine the nature of their functional arrest (Figure 2).[36] Cells from two patients failed to respond at the activation stage and from one at the proliferative stage (in addition to patients 108 and 112—the two patients with depressed activation responses). This is in agreement with studies by Chien and associates, who found activation unimpaired in B cells from patients with CVI.[40] All the patients' B cells failed to differentiate in the normal range, that is, an induced IgG and IgM response. Four patients did show partial responses to these differentia-

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tion drives (patients 109, 113, 125, and 143), which consisted primarily of enhanced IgM production.

This inability of patients' B cells to respond normally to differentiation signals suggested that altered responses to late-acting cytokines may play a role in the pathophysiology of this immune disorder. Although many cytokines influence the development of human B cells,[41,42] IL-6 or B-cell stimulatory factor 2 is particularly relevant for terminal B-cell differentiation. Interleukin 6 has been shown to drive the differentiation of B cells into high-rate Ig-secreting cells, to induce proliferation of Epstein-Barr virus-transformed cell lines and hybridoma cells in vitro, and to function as an autocrine growth factor for human myeloma cells.[43-46] In addition, IL-6 induces systemic effects similar to those of IL-1 and tumor necrosis factor. Interleukin 6 may even provide a potent stimulus for inducing autoimmunity.[47]

Because of the potential role of IL-6 in B-cell differentiation and growth as well as autoimmune phenomena, we tested the ability of CVI B cells to respond to IL-6. Blood B cells, however (as opposed to tonsil B cells), show minimal differentiation response to IL-6. Therefore, we took advantage of a series of human-human B-cell hybridomas that we had constructed (in collaboration with Randolph Wall, PhD) with either normal or CVI B cells.[48] These hybridomas manifest the functional phenotype of the immunodeficiency's expression of low levels of Ig μ messenger RNA with skewing toward the membrane form. When normal hybridoma B cells producing low levels of IgM were stimulated with IL-6, they showed an increase in IgM production consistent with a differentiation effect, whereas the hybridomas from the persons with CVI failed to do so (Figure 3). This deficit could be overcome by direct activation at the nuclear level using retinoids.[49,50] This indicates that the B cell in these patients does not carry an intrinsic defect in the nuclear read-out of the differentiation signal but in the events directly controlling responsiveness to immunophysiologic stimuli, such as IL-6. On a practical level, the successful restoration of B-cell differentiation by retinoids suggests their potential value as a therapeutic tool in common variable immunodeficiency.

Because of these findings, we investigated whether patients with this disorder had elevated serum levels of IL-6 resulting from their inability to differentiate in response to IL-6.[51] Serum IL-6 levels were elevated 3-fold to 18-fold above the normal range in 13 of 17 patients with CVI. In contrast, serum IL-6 levels were normal in patients with other B-cell immunodeficiencies (selective IgA deficiency and X-linked agammaglobulinemia). Interleukin-6 levels are controlled by a serum binding factor and the rate of IL-6 synthesis. We found that the serum binding factor activity was normal in patients with CVI. Spontaneous IL-6 produc-

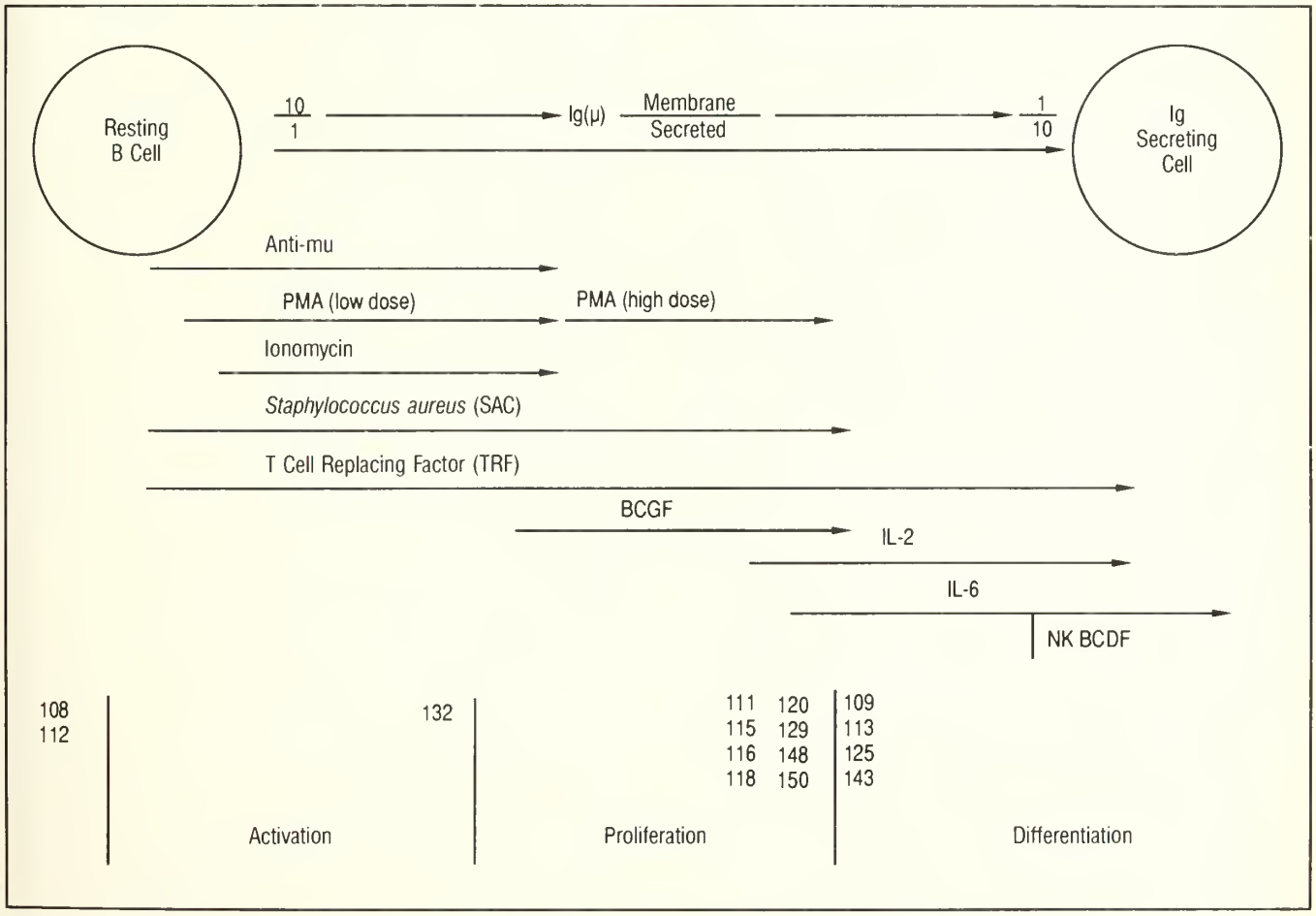

Figure 2.—A schematic is shown of B-cell development from resting B cells through activation, proliferation, and differentiation. The increased amount of messenger RNA for secreted versus membrane immunoglobulin (Ig) is represented in the upper section. Stimuli used in vitro for the different stages of development are shown in the middle section. On the bottom, the point where each patient's cells were unresponsive is represented by the UCLA immunodeficient patient's number. Most B cells failed to differentiate despite undergoing activation and proliferation normally (from Saxon et al[36]; adapted with permission from *Journal of Allergy and Clinical Immunology*). BCGF = B-cell growth factor, IL = interleukin, mu = IgM heavy chain, NK BCDF = NK cell-derived B-cell differentiation factor, PMA = 12-*O*-tetradecanoylphorbol 13-acetate

tion, however, by peripheral blood mononuclear cells from four patients with the immunodeficiency was significantly greater than by peripheral blood mononuclear cells from normal volunteers and a patient with hyper-IgM syndrome. Stimulated IL-6 production (by lipopolysaccharide) raised absolute IL-6 levels in normal persons to the unstimulated level in patients with CVI, suggesting that IL-6 production in these patients is endogenously at maximal levels. Although the endogenous stimulus of elevated IL-6 production in patients with CVI remains to be identified, these IL-6 levels may account for the clinical manifestations of lymphoproliferation and the autoimmune phenomena associated with this disease.

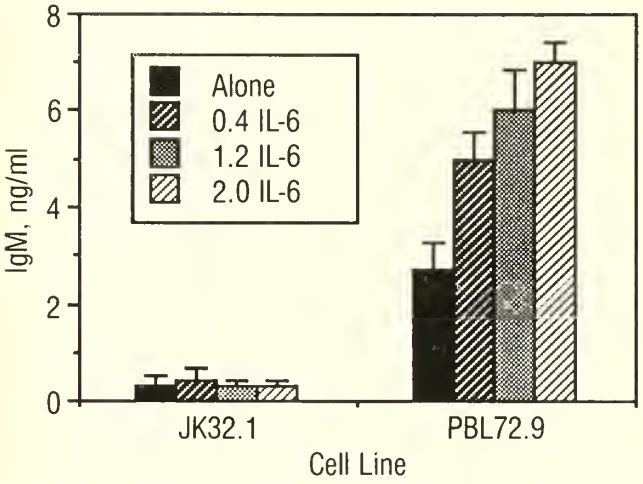

Figure 3.—Immunoglobulin (Ig) M production by common variable immunodeficiency (JK32.1) or normal (PBL72.9) hybridoma B cells is shown. Cells (10,000) were cultured for 3 days in 200 ml of complete medium alone or an increasing amount of recombinant interleukin 6 (IL-6). The amount of IgM in the supernatant at day 7 was measured by isotype-specific solid-phase enzyme-linked immunosorbent assay. The normal hybridoma cells show a clear dose response to IL-6, whereas this was not found with the common variable immunodeficiency cells. The error bars represent 1 standard deviation.

A Maturational Block at the Germinal Center Stage

Diverse functional abnormalities, such as those seen in CVI, raise the possibility that the disease actually involves a differentiative arrest at a specific stage in B-cell development. This idea was addressed by analyzing the expression of surface molecules known to be related to B-cell activation and maturation.[32] The striking difference between normal subjects and patients was a pronounced increase in the abundance of Leu-8^{dim} B cells, which also typically had elevated CD20 expression (Figure 4). A less striking but significant reduction in CD21 expression was also found. There was almost no overlap between 10 control subjects and the 15 patients with the disorder analyzed in this manner, and the abnormality was restricted to the B-cell population.

Remarkably, this unusual differentiation antigen phenotype of blood B cells in patients with CVI is in key respects the *normal* phenotype of B cells found in the germinal center, a critical site of memory B-cell development.[52] In addition, the unusual pattern of developmentally regulated B-cell clones (for example, V_H3_L) common to blood B cells in patients with CVI is that found with normal germinal center B cells (see preceding discussion by Braun). Moreover, a subpopulation of antigen-responsive B cells apparently representing recent germinal center emigrants[53] is profoundly deficient in patients with this immune deficit.[54] Taken together, these findings strongly suggest that B cells in most patients with CVI are arrested at a germinal center stage of differentiation.

The inability of these patients' B cells to proceed beyond this stage is consistent with the B cells' functional abnormalities in terminal differentiation and the corresponding deficits in qualitative and quantitative antibody production. The Leu-8 antigen is now known to represent a lymph node homing molecule,[55,56] and deficient expression may hinder effective lymphoid localization of B cells needed for antigen-specific responses. The CD20 molecule (a probable B cell-specific calcium channel) transmits a co-competence proliferative signal and may normally prevent cells from progressing through their differentiation pathway.[57] Its constitutive overexpression may thus directly contribute to the maturational arrest in CVI and perhaps to the associated B-cell hyperplasia and lymphoproliferative disease.

Thus, CVI may involve a relatively uniform pathophysiology related to a specific maturational arrest in B-cell development rather than a wide variety of disparate disease processes as previously thought. This primary defect remains to be defined and may include either an intrinsic unresponsiveness of B cells to the cytokines and regulatory cells found in the germinal center or to the dysfunction or destruction of these regulatory cell types. Secondary processes, such as the overexpression of IL-6 and possibly other potent

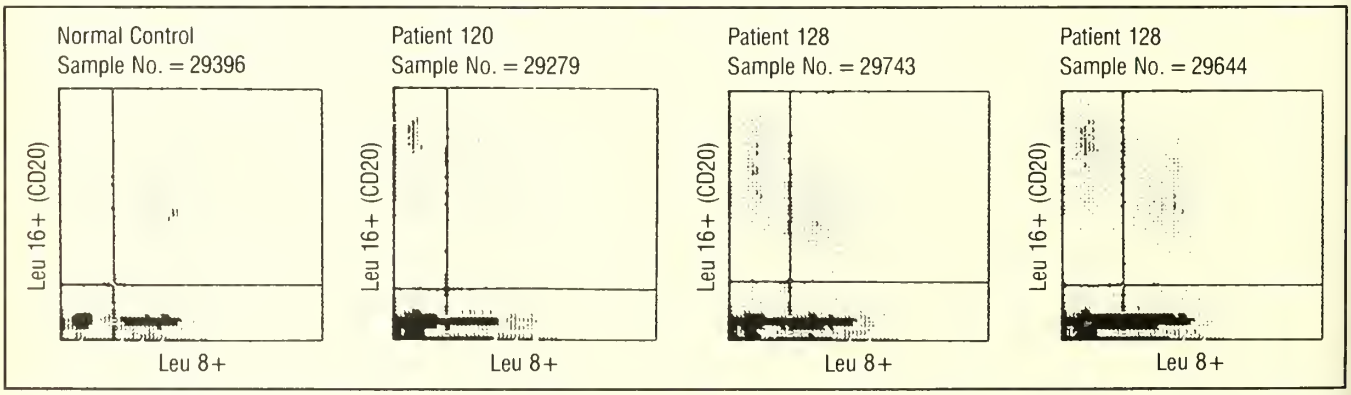

Figure 4.—Dual color flow cytometric analysis is shown of the expression of CD20 and Leu-8 on normal and common variable immunodeficiency (CVI) B cells. In a normal donor, only 10% of B cells (CD20$^+$) are Leu-8^{dim}. In contrast, in the subjects with CVI (120 and 128), most of the CD20$^+$ cells are Leu-8^{dim} (77% and 62%, respectively). Leu-8 expression in CD20$^-$ cells (mainly T cells) is unaffected. Compared with normal subjects, CD20 expression is also elevated in many CVI B cells. The right 2 panels show data from the same subject 4 months apart, showing the reproducibility of the staining pattern (from Saxon et al[36]; adapted with permission from *Journal of Allergy and Clinical Immunology*).

cytokines, may account in a large measure for the widely variable clinical phenotype of the disease.

Molecular Pathways in Immunoglobulin κ Light-Chain Gene Activation

RANDOLPH WALL, PhD*: Immunoglobulin heavy- and light-chain genes are rearranged and expressed at different stages in B-cell development.[58] Pre-B cells contain rearranged μ genes and synthesize Ig μ heavy chains.[59] When pre-B cells develop into B cells, light-chain genes are rearranged and expressed, and the light chains produced are assembled into membrane IgM.[60] This process involves the juxtaposition and activation of several transcriptional regulatory DNA regions found in the regions flanking the light-chain coding segments (Figure 5). The murine pre-B leukemic cell line,

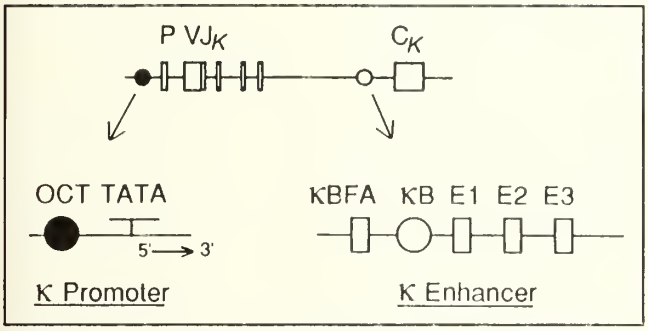

Figure 5.—The schematic shows the transcriptional regulatory elements found in promoter and enhancer regions of the immunoglobulin light-chain κ gene. See text for details.

70Z/3, has been extremely useful in defining the molecular events in Igκ gene activation.[61] The 70Z/3 cells contain an unrearranged κ-chain gene and a productively rearranged light-chain gene with a variable region (V_κ) joined to a joining region (J_κ) upstream of the constant region (C_κ).[62] These κ genes in 70Z/3 cells are normally not expressed. Both κ genes in 70Z/3 pre-B cells, however, are activated and expressed in response to bacterial lipopolysaccharide, IL-1, interferon gamma (IFN-γ), and several physiologic inducers, which mimic different intracellular second messengers.[61,63,64] I will focus on the lymphokine- or mitogen-inducible *trans*-acting factors that bind to κ enhancer DNA sequence motifs to control the developmental stage-specific activation of κ-gene transcription.

Lipopolysaccharide (LPS) induction of 70Z/3 cells results in the appearance of deoxyribonuclease hypersensitivity at a region in both κ genes[62] later shown to be the κ-gene enhancer.[59] The κ enhancer is now one of the best-studied transcription control segments of any mammalian gene. The κ enhancer contains multiple DNA sites that regulate light-chain gene transcription through their interaction with specific *trans*-acting DNA-binding proteins.[65] Some of these are constitutive regulators (for example, E1, E2, E3) that are not regulated by activation.[59,65] Others, such as the κB DNA and κBF-A, are key sites in the induction of κ gene transcription by endotoxin (LPS) and IL-1.[66,67]

The first clue to the molecular processes in κ induction by LPS came from studying the requirements for new macromolecular synthesis in LPS-induced κ-gene transcription in 70Z/3 pre-B cells. It was found that the protein synthesis inhibitor, cycloheximide, failed to block κ induction by LPS.[68] In fact, treatment of 70Z/3 cells with cycloheximide alone activated the transcription of κ genes.[68] This unexpected finding showed that LPS induction of κ-gene transcription occurred through a novel post-translational mechanism involving the activation or modification of existing cell proteins. We predicted that κ-gene expression in untreated 70Z/3 pre-B cells was blocked by labile inhibitory protein(s) and that induction by LPS (or cycloheximide) activated κ transcription by causing turnover of the labile inhibitor(s).

Sen and Baltimore subsequently determined that the induction of κ transcription by LPS and cycloheximide occurred through the post-translational activation of the κ enhancer binding factor, NF-κB.[69] Interleukin 1, PMA (12-*O*-tetradecanoylphorbol 13-acetate), and cyclic adenosine monophosphate (cAMP) analogues also activate NF-κB transcription factor binding to the κB DNA motif.[66] This factor exists in the cytoplasm of uninduced cells in an inactive state complexed to an inhibitor called IκB.[70] Strong evidence indicates that NF-κB activation occurs through protein kinase-mediated phosphorylation of the labile IκB inhibitor.[66] This phosphorylation is activated through distinct intracellular signaling pathways involving either protein kinase C (activated by LPS or PMA) or cAMP-dependent protein kinase (activated by IL-1).[66] NF-κB also can be activated by protein synthesis inhibitors like cycloheximide, presumably through a turnover of the IκB inhibitor.[66,70] Thus, the IκB inhibitor[70] defined by Sen and Baltimore[69] is likely to be the labile inhibitor of κ-gene expression proposed in our earlier study.[68]

Two lines of evidence from our laboratory indicate that NF-κB activation is only one of several collaborative molecular events needed for κ induction after LPS (or IL-1) induction. With Paul Kincade, PhD (Oklahoma Medical Research Foundation), we found that transforming growth factor β (TGF-β) efficiently blocked κ induction.[71] We then determined that NF-κB activation and binding occurred normally in the presence of TGF-β,[72] indicating that the TGF-β sensitive step in κ induction parallels or follows NF-κB activation. The recently discovered LPS-induced factor, κBF-A, provides a compelling candidate target for the inhibitory effect of TGF-β because κBF-A activation follows the early induction of NF-κB binding directly after LPS stimulation.[67]

The second line of evidence comes from our studies analyzing the molecular defects in 70Z/3 mutant cell lines, which are unresponsive to LPS and other inducers used to activate κ-gene transcription. We found two classes of LPS-unresponsive mutants with regard to NF-κB function and activation of κ transduction. One class (composed of three 70Z/3 variant lines) contains functional NF-κB factor (as shown by in vitro activation with detergent), which cannot be induced in vivo by any agent.[73] These variants seem to be defective in the intracellular signaling events leading to IκB phosphorylation. This has been confirmed by showing that purified cAMP-dependent protein kinase added to variant cell extracts activates NF-κB in vitro. In the second class of unresponsive mutant 70Z/3 cells (represented by one 70Z/3 variant cell line), NF-κB is activated normally by LPS, but κ expression is not induced. The behavior of this latter mutant line clearly mimics the inhibitory effect of TGF-β. The defect in this class of LPS-unresponsive 70Z/3 mutant cells may affect κBF-A activation. Experiments in progress are directed at determining if LPS-induced κBF-A binding to the

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κ enhancer is inhibited by TGF-β or deficient in this second class of variant 70Z/3 cells that activate NF-κB normally.

Interferon gamma is another potent inducer of κ-gene transcription in 70Z/3 cells.[61] Unlike LPS and other inducers, however, κ induction by IFN-γ is not affected by TGF-β.[71] Because of this, it seemed likely that NF-κB might not be induced by this lymphokine. Subsequent experiments confirmed that NF-κB is not activated in 70Z/3 cells expressing κ after IFN-γ induction.[72] These results indicate that the induction of κ transcription by LPS (or IL-1) proceeds by a different molecular pathway than that used by IFN-γ. The finding that mutant cell lines of 70Z/3, selected for a loss of responsiveness to LPS, retain inducibility of κ expression by IFN-γ[73] is consistent with this proposal.

What DNA sequences control κ-gene induction by IFN-γ? One candidate is the octamer motif in the κ promoter, which binds a transcription factor found in all cells (called oct-1) and an LPS-induced factor restricted to B cells (called oct-2).[74] The genes encoding the oct-1 and oct-2 factors have been cloned,[74] but it is unlikely that the oct-2 factor is involved in IFN-γ induction because it is not increased by IFN-γ treatment.[72] A promising candidate DNA sequence for mediating IFN-γ induction of κ transcription is the κBF-A site in the κ enhancer, which is notably similar to a DNA sequence motif known to be involved in IFN-γ induction of major histocompatibility complex class I genes and shown to bind IFN-γ–induced *trans*-acting factors. We have recently determined that this sequence in the κ enhancer binds an IFN-γ–induced factor, which is different from the LPS-induced κBF-A factor binding to this same sequence (R. Wall, PhD, unpublished data, June 1991). This new finding suggests that LPS and IFN-γ activate different *trans*-acting DNA-binding factors that bind to the same DNA sequence. This mimics the situation with the octamer DNA motif whose activity is determined by different DNA-binding factors reacting with one DNA sequence.[74]

Even with the present state of knowledge of the molecular events in κ light-chain gene activation, several issues remain to be resolved before the different molecular pathways to κ-gene expression are fully delineated. B cells and plasma cells, which constitutively express κ genes,[66] contain an active DNA-binding form of NF-κB. It is not known how this constitutively activated form of NF-κB is generated. The recent finding of a second κ enhancer segment located far downstream of the C_κ region adds further complexity to be resolved.[75] Clearly studies on the κ enhancers and their roles in κ induction and expression will continue to yield interesting surprises.

Genetically Engineered Antibody Molecules

SHERIE L. MORRISON, PhD*: Antibodies have long been appreciated for their specificity in binding their ligand, an antigenic determinant. Because of this specificity, antibodies seem ideal for discriminating between the minor differences that occur between cell-surface antigens of tumor cells versus normal tissues. A second, perhaps equally important, characteristic of antibody molecules is their ability to carry out biologic effector functions, such as complement activation and antibody-dependent cellular cytotoxicity. The combining specificity of the antibody molecule can therefore be used to target these naturally occurring effector functions to particular cellular or subcellular locations. Alternatively, antibodies can be used to deliver cytotoxic agents.

Antitumor antibodies were initially obtained from immunized animals, but because different antisera represented pools of heterogeneous antibodies with differing specificities and effector functions, it was difficult to carry out reproducible studies using serum as the source of antibodies. A significant breakthrough was the development of the hybridoma technology, whereby it became possible to generate a potentially endless supply of monoclonal antibodies of defined binding specificity.[76]

Even the monoclonal antibodies produced by hybridoma cell lines, however, have some properties that make them less than ideal: It has been difficult to produce monoclonal human antibodies,[76] and the isotype of the resulting antibodies often is inappropriate for the desired biologic properties.[77] Genetically engineered antibodies produced by expressing cloned genes in the appropriate cell type provide an approach for producing antibodies with superior properties. It is now possible to produce chimeric antibodies with gene segments derived from diverse sources. Because genes can be modified before they are expressed, constant regions with improved biologic properties can be produced. In addition, molecules that bind antigen, but that are never found in nature, such as fusions of antibodies with nonantibody proteins, can be manufactured.

All antibodies have a basic structure of two pairs of identical heavy (H) and light (L) chains joined together by disulfide bonds to form a bilaterally symmetric structure (Figure 6). The polypeptide chains fold into globular domains separated by short peptide segments. The *N*-terminal domain of each chain constitutes the variable region that carries the antigen combining site, which determines the specificity of the antibody. The remainder of the antibody constitutes the constant (C) region, which is responsible for the effector functions, such as Fc-receptor binding, complement fixation, catabolism, and placental transport. Immunoglobulins with different constant regions and therefore of differing isotypes—in humans they are IgM, IgD, IgG1-4, IgA1, IgA2, and IgE—show different biologic properties. In some isotypes a hinge region separates C_H1 and C_H2 and provides the molecule with segmental flexibility. Antibodies are glycoproteins with the carbohydrate content varying among different isotypes. One uniform feature of all IgG isotypes is that each H chain contains a single carbohydrate moiety at Asn 298 in C_H2, which is essential for some effector functions.

Antibodies are unusual proteins in that the genes that encode them must be somatically assembled to produce a functional protein. For a variable region to be expressed, a rearrangement of DNA must take place and the expressed variable region positioned next to a J segment for the L chain or a DJ segment for the H chain. The domain structure seen in the antibody molecule is reflected in the structure of the genes that encode it, with each antibody domain being encoded by a discrete exon (Figure 6).

One approach to producing improved antibody molecules is to use recombinant DNA techniques and gene expression to produce antibodies with improved antigen binding specificities and effector functions. An advantage of this approach is not being limited to producing antibodies as they exist in nature. Instead, antibody molecules can be designed to have optimized properties, such as binding specificity pharmacokinetics, and effector functions, such as complement activa-

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tion and Fc-receptor binding. In addition, novel functions can be introduced into the antibody molecule that are not normally found there. Mouse-human chimeric antibodies, in which the variable region is derived from a murine hybridoma cell line and the constant regions are human, provide reagents with reduced immunogenicity when used in vivo in humans.

To produce genetically engineered antibody molecules, the following must be available:

- A recipient cell that will produce a functional antibody molecule;
- A means to efficiently introduce DNA into the recipient cells; and
- Expression vectors that permit the expression of the antibody genes and the isolation of the rare recipient cells expressing the introduced genetic information.[78]

Gene transfection into eukaryotic recipients is one way to produce genetically engineered antibodies.[77] Appropriate mammalian cells for immunoglobulin gene expression are myeloma and hybridoma cell lines, which are capable of high-level expression of endogenous heavy- and light-chain genes; these cells lines can also glycosylate, assemble, and secrete functional antibody molecules. Transfected genes are not always expressed at the level found in hybridomas and myelomas. When all of the important features controlling the expression of transfected genes are understood, however, there is no reason that high levels of antibody expression by gene transfection cannot be achieved routinely. Several myeloma cell lines are available for gene transfection and expression. The cell lines routinely used to produce transfectoma cell lines are the non-Ig-producing hybridoma cell-line parents, SP2/0 and P3X63.Ag8.6.5.3.

Several methods are available for introducing foreign DNA into eukaryotic cells. Although lymphoid cells are inefficient in taking up and expressing calcium phosphate-precipitated DNA, both electroporation[78] and protoplast fusion[79,80] are effective methods of introducing genes into lymphoid cells. There is variability in transfection frequency between different lymphoid cell lines and even between clones of the same cell line. With both electroporation and protoplast fusion, transfection frequencies between 10^{-3} and 10^{-6} can be achieved routinely. Thus, it is feasible to isolate the desired transfectant cell line or transfectomas.

Even under optimal conditions, gene transfection into eukaryotic cells is an inefficient procedure, with only rare recipient cells becoming stably transfected. Thus, vectors must be used that contain biochemically selectable markers, which permits the selection of the rare, stably transfected cell lines. The most commonly used markers are genes derived from bacteria that permit cells expressing them to survive in the presence of particular drugs. These markers are dominant drug-resistance markers; that is, the expression of their phenotype is a dominant trait, and they can be used in cells that have not been drug-marked previously. The bacterial genes used in these vectors are provided with a viral (SV40) promoter, splice junction, and polyadenylate addition signal so that they can be expressed in eukaryotic cells. The bacte-

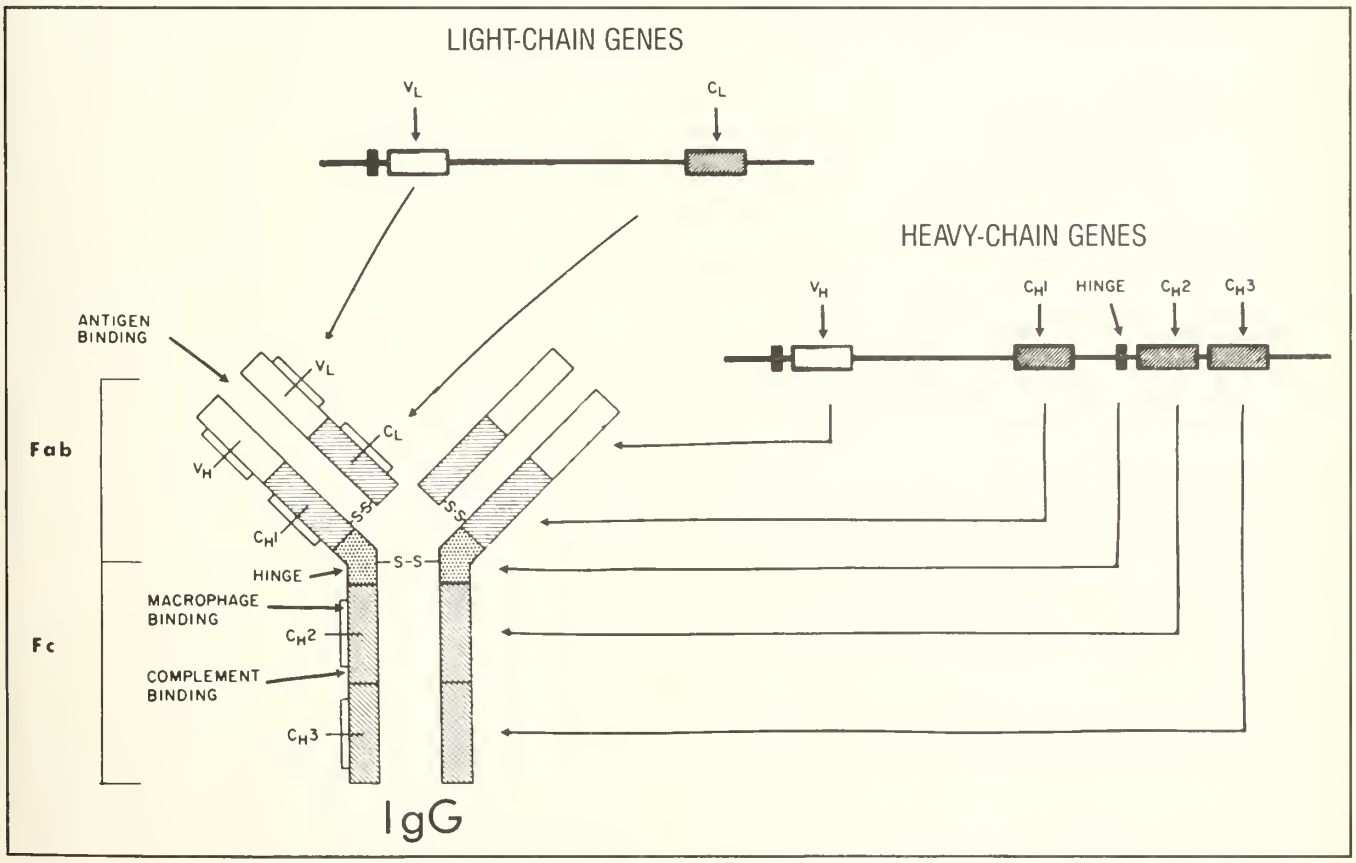

Figure 6.—The structure of an immunoglobulin molecule and the genes that encode it is shown. The regions of the molecule that participate in antigen binding (Fab) or different effector functions (Fc) are indicated. The arrows show the correspondence between the DNA segments and the different domains of the immunoglobulin polypeptide chain that they encode. The hydrophobic leader sequence of both heavy and light chains is removed immediately after synthesis and is not present in the mature immunoglobulin molecule (from Morrison[77]; reproduced with permission from *Science*).

rial genes usually used include the phosphotransferase gene from the Tn5 transposon (designated *neo*),[81] the xanthine-guanine phosphoribosyltransferase gene (*xgprt* or *gpt*),[82] and genes encoding key steps in the synthesis of essential amino acids, *his* and *trp*.[83]

To obtain DNA in sufficient quantities for genetic manipulation, it is essential that the vectors can be propagated as plasmids in bacteria. To achieve this objective, the original plasmids contain the origin of replication and β-lactamase gene from the plasmid pBR322. Bacteria propagating these plasmids can be selected for their resistance to ampicillin. A second family of vectors contains the origin of replication from the plasmid pACYC184 and the chloramphenicol acetyltransferase gene[84]; these plasmids are propagated in bacteria selected for resistance to chloramphenicol. With both vectors, it is easy to obtain large quantities of DNA for in vitro manipulation. Because pBR322 and pACYC184 have compatible replication origins, both plasmids can be maintained together at high copy number within the same bacterium. When protoplast fusion is used, both vectors can be introduced simultaneously into a recipient cell.

To create functional antibody molecules, the genes encoding heavy and light chains must be transfected into the same cell, and both polypeptides must be synthesized and assembled. Several methods have been used to achieve this objective. Both the heavy- and light-chain genes have been inserted into a single vector and then transfected[85]; this approach generates large, cumbersome expression vectors, and further gene manipulation of the vector is difficult. A second approach is to transfect sequentially the heavy- and light-chain genes, using different drug resistance markers to select for the expression of the different vectors.[86] Sequential selection of transfectants is time-consuming. Alternatively, both genes can be introduced simultaneously on different DNA fragments using either electroporation or protoplast fusion and using the compatible plasmid vectors described earlier; this approach is usually the most efficient in creating complete antibody molecules.

To produce antibodies of interest, it is necessary to obtain the gene sequences for the variable regions of interest and then to join them to the appropriate constant region in an expression vector. The variable regions desired for expression can be obtained from the appropriate antibody-producing cell line as either complementary DNA or genomic clones. By obtaining variable regions from human antibody-producing cell lines, it is possible to produce completely human antibodies. Thus, this approach is also appropriate for rescuing low-production human hybridomas and lymphoblastoid lines and for obtaining isotype switch variants of human immunoglobulin genes.

A major reason for developing Ig gene transfections and expression systems is to be able to engineer and express novel hybrid, chimeric, and mosaic genes using recombinant DNA techniques. This technology should have an important effect on our understanding of the structures and mechanisms involved in the biologic functions of antibody and should provide invaluable reagents.

Genomic clones of Ig variable- and constant-region genes are easy to manipulate using genetic engineering techniques because of their division into exons. The distinct Ig polypeptide domains are each encoded by a discrete exon; for example, the variable and constant domains of the light chain, the variable region, the hinge, and the three constant-region domains of the IgG heavy chain are each encoded by distinct exons. The intervening DNA sequences (introns) separating each domain provide ideal sites for manipulating the antibody gene shown in Figure 6. Because the intervening sequences are removed by splicing from the mature mRNA, alterations within them will not affect the structure of the protein. In addition, the RNA splice junction between variable- and constant-region exons in heavy- and light-chain genes is conserved, making it easy to manipulate the Ig structure by deleting, exchanging, or altering the order of exons.

The exon structure of the Ig gene can be exploited to construct antibody-cassette expression vectors. Oligonucleotide linkers can be used to flank the constant-region exons with unique restriction sites.[84] In addition, linkers can be placed between the domains of the human IgG heavy-chain genes, making exon and domain shuffling of these straightforward.[86] Oligonucleotide-directed mutagenesis can also be used to produce mutations in the Ig genes.

Biologic effector functions, such as complement fixation, antibody-dependent cellular cytotoxicity, and Fc-receptor binding, are mediated by the heavy-chain constant region, and different isotypes have different biologic properties. Although some structures important for these activities have been defined, the exact molecular correlates of many antibody effector functions remain unknown. With the availability of recombinant DNA technology and gene transfection, the study of structure-function relations within the antibody molecule can now be approached systematically. Chimeric proteins in which the murine variable region is expressed joined to different human constant regions show the biologic properties previously defined for naturally occurring nonchimeric antibodies. Therefore, chimeric antibodies can be used to determine the amino acid sequences responsible for the effector functions of antibody molecules. The ultimate objective of these experiments is to design and produce human immunoglobulin molecules with improved effector functions.

All IgG molecules contain a consensus glycosylation sequence (Asn-X-Thr-, where X represents any amino acid) in the C_H2 domain. The presence of this carbohydrate is important for some of the effector functions of Ig, including Fc-receptor binding and complement activation[87]; however, aglycosylated antibodies are properly assembled, secreted, and bind antigen and *Staphylococcus* protein A. The serum half-life in mice of an aglycosylated chimeric human IgG1 was the same as the wild type (6.5 days), but aglycosylated IgG3 has a shorter half-life (3.5 days) than does wild-type IgG3 (5.1 days). Thus, the absence of carbohydrate profoundly changes some properties of the antibody molecule while leaving others intact.

A property of antibody molecules critical for their in vivo function is the ability to bind to cellular Fc receptors. Chimeric IgG1 and IgG3 bind the high-affinity Fc receptor (IgFcg1) with a binding constant of 1×10^{-9} mol per liter^{-1}; chimeric IgG4 binds with approximately tenfold reduced affinity, and binding by chimeric IgG2 is not detectable. Using site-directed mutagenesis, residue 235 of mouse IgG2b has been pinpointed as interacting with this Fc receptor.[86] Equivalent experiments are in progress with chimeric human antibodies.

Novel proteins that possess the binding specificity of antibody molecules can be created by replacing the constant-region DNA sequence of an Ig molecule with a sequence

derived from another molecule, such as an enzyme, toxin, growth factor, or other biologic response modifier.[89-92] Such molecules have potential use in immunoassays, diagnostic imaging, and immunotherapy.

The possible uses of genetically engineered monoclonal antibodies are many. Perhaps the most immediate advantage of chimeric monoclonal antibodies will be the reduction of the human antimurine antibody response. The human antimurine response creates two problems: the potential of an allergic response with anaphylaxis and the rapid clearance of the administered antibody, preventing most of the antibody from reaching the tumor site. Another advantage of chimeric antitumor antibodies is the potential for enhancing effector cell killing and complement-mediated tumor cell killing. By using genetically engineered monoclonal antibodies, it is also feasible to modify the Ig molecule to alter pharmacokinetics. The plasma clearance of an unconjugated antibody can be slowed down so that it will have the opportunity to mediate antibody-dependent cellular cytotoxicity or complement-mediated cytolysis, or speed up the plasma clearance of a monoclonal antibody conjugated to a radioisotope, in which the circulating conjugate may cause damage to normal cells.

Finally, antitumor monoclonal antibodies may be modified so that they can act as more efficient vehicles for the delivery of antitumor drugs, toxins, radionuclides, or biologic response modifiers. This can be achieved either by directly ligating the antitumor agent into the Ig molecule or by ligating efficient linkers for drugs, radioisotopes, or bioresponse modifiers into the Ig molecule.

Many possible applications of chimeric or genetically engineered antibodies exist in addition to their use as anticancer agents. Monoclonal and chimeric antibodies to cell surface antigens have been produced that are important for immune interactions. These antibodies have great potential as immune response modifiers to facilitate organ transplantation and address problems of autoimmunity. It is also possible that antibodies may be developed to approach the problem of immune nonreactivity, such as is seen in the acquired immunodeficiency syndrome. Chimeric antibodies also may have applications in the treatment of infectious diseases where they should be far superior to antiserum derived from heterologous sources and should address the heterogeneity and limited availability of antiserum derived from human sources. Chimeric antibodies also have great potential for use as vaccines devised to exploit the anti-idiotypic network. The possible uses of chimeric antibodies and antibodies modified by recombinant DNA techniques are limited only by the imagination of the investigators exploiting this family of reagents.

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Epitomes

Important Advances in Clinical Medicine

Chest Diseases

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in chest diseases. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, or scholars to stay abreast of these items of progress in chest diseases that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Chest Diseases of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Occupational Asthma

While the overall prevalence of occupational asthma is unknown, it is estimated that from 5% to 15% of all cases of asthma in workers is attributable to workplace exposures. Occupational asthma can be defined as a variable airflow limitation caused by a specific agent in the workplace. Variable and sometimes chronic airflow limitation can result from sensitization to, pharmacologic effects of, recurrent inflammation from, or direct irritation by agents in the workplace. The treatment of occupational asthma may differ depending on its cause. The cornerstone of management is early diagnosis and identification of the offending agent, but diagnosis is not easy and often involves the investigation of exposure conditions at the workplace combined with an objective confirmation of exposure-related changes in lung function.

It is a common misconception that occupational asthma caused by a worker's sensitivity to a specific agent—for example, toluene diisocyanate or laboratory animal protein—resolves after the worker is removed from further exposure to that agent. Although occupational asthma often resolves with this intervention, the results of several longitudinal studies indicate that most persons continue to have some degree of persistent asthma years after removal from exposure. Factors associated with a more favorable result are a short duration of symptoms before diagnosis and relatively normal lung function and mild, nonspecific airway hyperresponsiveness at diagnosis. Early diagnosis and removal from exposure may prevent or lessen persistent asthma and the resulting impairment or disability.

Workers who continue in jobs that expose them to an agent to which they are sensitized tend to have increased respiratory symptoms, a progressive loss of ventilatory function, and increased airway responsiveness. This deterioration may occur despite suppressing symptoms with medication or reducing the intensity of exposure by using respiratory protective gear. Several deaths have been reported among workers with isocyanate-induced asthma who continued to work in jobs that involved exposure to that agent.

Some patients with occupational asthma cannot change jobs because of financial constraints. In such cases, vigorous efforts to reduce exposure to the lowest possible level are required. Product substitution, enclosure of specific work processes, and improved ventilation are preferable to the use of respirators, which are cumbersome, uncomfortable, and may leak. If respirators are to be used, however, patients must be medically certified, fit-tested, and properly trained to wear them. Careful monitoring can help assess the effectiveness of interventions to reduce exposure. Serial measurements of peak expiratory flow rates can document any recurrent subclinical bronchospasm, and serial methacholine challenge can assess whether the level of airway responsiveness is increasing. Patients with evidence of bronchospasm or an accelerated annual rate of decline in ventilatory function should be strongly encouraged to change jobs.

Drug therapy for occupational asthma is the same as that for persons with nonoccupational asthma, but treatment with drugs cannot substitute for eliminating exposure.

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Antibiotics for Pneumonia

Acute pulmonary infection continues to cause substantial morbidity and mortality even in immunocompetent patients. Although a sputum Gram's stain may be immediately available and, if of good quality and showing a predominant organism, may help focus therapy, rapid and definitive identification of the specific etiologic agent(s) responsible for a pneumonia is often difficult. For these reasons, empiric antibiotic therapy is usually instituted concurrent with attempts at diagnosis. Epidemiologic factors are helpful in choosing a reasonable regimen.

A recent multicenter study of patients admitted for community-acquired pneumonia to a private community hospital, a university hospital, and a Department of Veterans Affairs hospital reported the four most common etiologic

agents to be *Streptococcus pneumoniae* (15.3%), *Haemophilus influenzae* (10.9%), *Legionella* species (6.7%), and *Chlamydia pneumoniae* (6.1%). These findings strongly support including erythromycin in the empiric antibiotic treatment of community-acquired pneumonia. Two new macrolide antibiotics, clarithromycin and azithromycin, may be better tolerated and as effective as erythromycin in treating legionella, chlamydial, and mycoplasmal infections, although they are sevenfold more expensive.

Other pathogens responsible for community-acquired pneumonia are more common in specific patients. *Staphylococcus aureus* is observed in nursing home residents and following influenza infection. *Moraxella (Branhamella) catarrhalis* causes pneumonia in older patients and those with obstructive lung disease. Erythromycin generally is effective as the initial empiric therapy for infection with these organisms. More specific therapy for *M catarrhalis* and *H influenzae* includes the combination drugs amoxicillin and potassium clavulanate, ampicillin and sulbactam sodium, trimethoprim and sulfamethoxazole, ciprofloxacin, or a third-generation cephalosporin. Aerobic gram-negative bacilli are seen more commonly in older patients, those who use alcohol, and those with obstructive lung disease. Ciprofloxacin is not an ideal choice for empiric coverage of pneumonia because of marginal activity against *S pneumoniae*. In a severely ill or immunocompromised patient with community-acquired pneumonia of unknown origin, gram-negative bacilli must be covered.

Most pneumonias that develop in immunocompromised and hospital patients are caused by aerobic gram-negative bacilli. The most common agents are those of the family Enterobacteriaceae—*Klebsiella pneumoniae, Escherichia coli, Enterobacter* species, and *Serratia marcescens*—and *Pseudomonas* species. Several third-generation cephalosporins have excellent activity against these organisms and are good choices for these patients. Current evidence continues to support using a semisynthetic penicillin (piperacillin sodium) or a third-generation cephalosporin (ceftazidime) in synergistic combination with an aminoglycoside to treat pseudomonad infections. *S aureus* may be seen in the nosocomial setting and should be covered with initial therapy or if gram-positive cocci are observed in pulmonary secretions. Many third-generation cephalosporins such as ceftizoxime provide *S aureus* coverage. If methicillin-resistant *S aureus* is present in the hospital, vancomycin hydrochloride should be used in initial empiric regimens.

Aspiration pneumonia occurring in the community may be treated effectively with penicillin, but the increasing incidence of resistant *Bacteroides* species makes clindamycin hydrochloride a more reliable choice. Patients in hospital have high rates of colonization of the oropharynx and gastrointestinal tract with gram-negative bacilli. Antibiotic therapy for aspiration in the hospital must cover the usual nosocomial organisms as well as anaerobic pathogens; monotherapy with a third-generation cephalosporin such as ceftizoxime is reasonable empiric coverage.

Pneumonia caused by *Pneumocystis carinii*, viruses, and fungi (*Aspergillus* species, *Candida* species) may also develop in immunocompromised patients, requiring agents not typically included in initial empiric regimens. A recent randomized trial has shown that therapy with broad-spectrum antibiotics plus trimethoprim-sulfamethoxazole and erythromycin was as effective as and caused fewer complications than open-lung biopsy in cancer patients with diffuse pulmonary infiltrates. It is accepted practice to add empiric antifungal therapy for neutropenic patients who do not respond to treatment with antibacterial agents after several days.

In all settings, when a specific etiologic agent is identified, antimicrobial therapy should be narrowed to avoid superinfection and the selection of drug-resistant bacteria. With regard to preventing nosocomial pneumonia in critically ill patients, a recent well-controlled study has shown that selective decontamination of the digestive tract does not improve survival in intubated patients receiving mechanical ventilation in intensive care units.

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Diagnosis of Pulmonary Embolism

THE ACTUAL INCIDENCE and natural history of pulmonary embolism are unknown. Perhaps 30% of patients are symptomatic and have substantial morbidity and mortality. Diagnosis is essential because treatment is thought to reduce mortality. Symptoms and signs are nonspecific, and examination of leg veins is helpful only infrequently.

Pulmonary angiography is the gold standard for diagnosis but is invasive, often inconvenient, and, in some institutions, done too infrequently to approach the accuracy reported from major centers. Noninvasive screening includes radionuclide lung scanning and examination of the leg veins by impedance plethysmography and duplex ultrasonography. The positive predictive value of any test, however, is a function of the clinical probability that the condition exists.

Lung scanning is an excellent screening test. A normal scan predicts with almost 100% probability that pulmonary embolism has not occurred. Contrariwise, a high-probability scan is associated with thromboembolism in 50% to 90% of patients. The probability of a true-positive is a function of the clinical science probability. Unfortunately, a high-probability scan is seen in only 10% to 15% of patients and is, therefore, nonsensitive. The dilemma is how to proceed when the scan is intermediate, indeterminate, or of low probability in a patient with at least a moderate risk for pulmonary embolism.

A useful approach is to examine the leg veins with impedance plethysmography or duplex ultrasonography. The sensitivity and specificity of these tests in patients with symptoms of deep-vein thrombosis is reported to be in excess of 90%. In asymptomatic patients after a hip operation, impedance plethysmography was found to have an unacceptably low sensitivity of 24%. Another series found that 30% of patients with angiographically demonstrated pulmonary emboli had normal leg venograms.

If a patient has a moderate likelihood of pulmonary embolism, an intermediate- or low-probability scan, and negative leg vein studies, do we proceed with pulmonary angiography or do we observe? A report from Canada suggests that if leg

vein studies remain negative in this cohort, treatment can be safely withheld. These investigators do emphasize the need for serial leg vein studies and also call for confirmation of their findings.

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Thrombolytic Treatment of Pulmonary Embolism

OVER THE PAST SEVERAL YEARS, there has been renewed interest in the use of thrombolytic therapy for treating venous thromboembolic disease. This is a consequence of both the availability of new thrombolytic agents and the interest in clot dissolution prompted by advances in treating coronary thrombolysis.

At present, the Food and Drug Administration has approved three thrombolytic agents for the treatment of pulmonary embolism: streptokinase, urokinase, and recombinant tissue plasminogen activator (rt-PA). Only streptokinase has been approved for treating deep venous thrombosis. All of these agents lower fibrinogen, plasminogen, and α_2-antiplasmin levels and generate a systemic lytic state. Fibrin selectivity has not yet proved to be of clinical importance nor has it been associated with lower rates of bleeding complications. Cost does differentiate among the several available thrombolytic agents. Although total costs vary with the duration of therapy, the total amount of the thrombolytic agent administered, the varied requirements for monitoring and blood work that different patients and protocols necessitate, and the occurrence and cost of complications, streptokinase is the least expensive of the available agents.

According to the standard protocols for treating venous thromboembolism, streptokinase and urokinase are administered by continuous intravenous infusion for periods of 12 to 72 hours, whereas tissue plasminogen activator is given as a 100-mg dose over 2 hours. Despite these recommendations, it is clear the optimal dosing regimens and duration of thrombolytic treatment have not yet been established. For continuous infusion therapy, setting the duration of therapy by the clock makes little sense; once thrombolytic treatment is initiated, it should be continued until either all clot amenable to thrombolysis has been dissolved or a complication of the therapy has been identified. One possible approach is to monitor the level of fibrin-degradation products (fibrin-split products), continuing thrombolytic treatment until levels are normal, indicating the cessation of notable clot lysis. For rt-PA, it is not clear if the short duration of therapy—based on the coronary thrombolysis model—is always sufficient to lyse the relatively large clot volume found in substantial pulmonary emboli and proximal deep venous thrombosis.

Current studies of the regimens for thrombolytic treatment of pulmonary emboli take into account the differences between the circulating half-lives of the thrombolytic agents (less than 25 minutes) and the duration of fibrinolytic activity within the thrombus (as long as 6 hours). Combining the duration of pharmacologic effects with the observation that an increased diffusion of thrombolytic agents into thrombus takes place when high circulating drug levels are present has led to the development of bolus-dosing protocols for treating pulmonary emboli with thrombolytic agents. Studies of animals and initial clinical trials with both urokinase and tissue plasminogen activator suggest that this approach may be more efficacious, with possibly less risk of sustained bleeding than the standard continuous infusion regimens.

Many investigators think that thrombolytic therapy should be used to treat any pulmonary embolus causing hemodynamic instability or respiratory compromise. More recently, some have proposed using echocardiography to evaluate large pulmonary emboli in stable patients; any evidence of right ventricular dysfunction or dilation is used as a rationale for treating with thrombolytic agents. This approach is currently being evaluated in a randomized trial.

A decade ago it was reported that the diffusing capacity of the lungs for carbon monoxide in patients treated with thrombolytic therapy was better preserved than in those treated with heparin. The explanation was that the pulmonary capillary blood volume (pulmonary microcirculation) is better preserved after thrombolytic therapy than after standard heparin anticoagulation. A preliminary report of follow-up hemodynamic examinations of these patients found that those treated with thrombolytic agents had lower mean pulmonary arterial pressures and pulmonary vascular resistance at rest and during exercise than did those who had been treated with heparin. The significance of the modest hemodynamic differences is unclear, however, and the question of whether the routine use of thrombolytic therapy for less substantial pulmonary emboli is appropriate to preserve the pulmonary microcirculation remains unanswered.

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Lung-Assist Devices

TWO KINDS OF DEVICES are used to assume the gas-exchange task of the lung. The first is an artificial lung, which is needed in part because of the lack of a suitable supply of healthy lungs for transplantation. The second is a lung-assist device to bridge the gap until lung transplantation can be accomplished. It is also used in patients with a severe abnormality in the gas-exchange process, as in the adult respiratory distress syndrome. Lung-assist devices may also help reduce intrathoracic pressure when patients are on mechanical ventilation, possibly resulting in decreased morbidity and mortality associated with the adult respiratory distress syndrome. The two approaches to lung-assist devices currently being evaluated are extracorporeal carbon dioxide removal and intravascular oxygenator.

In 1974 the National Institutes of Health funded a study on the efficacy of extracorporeal membrane oxygenation in

the adult respiratory distress syndrome. The control group was treated with mechanical ventilation and positive end-expiratory pressure. The result in both groups was about 10% survival, leading to the conclusion that extracorporeal membrane oxygenation has no role in this disorder. In the early 1980s, neonatologists had better success in the treatment of neonatal respiratory distress syndrome, with an overall survival rate reaching 78%.

Several recent European reports have suggested that the survival rate for patients treated with extracorporeal membrane oxygenation who met the entry criteria of the original 1974 study was close to 50%, reviving interest in lung-assist devices. There have been several important improvements in the technology, such as thromboresistant coating of the surfaces used, improved efficiency of membranes, and better pumps to reduce hemolysis and platelet destruction. The major change was that extracorporeal membrane oxygenation was modified into extracorporeal CO_2 removal. In the former procedure, blood completely bypasses the heart and the lungs. This technique is designed to support the failing lungs and heart. In extracorporeal CO_2 removal, blood is drained from and returned to the vena cava after membrane gas exchange, therefore only supporting the lungs. Extracorporeal CO_2 removal also allows the use of low-frequency mechanical ventilation, low positive end-expiratory pressure, and continuous low-flow oxygen, but oxygen uptake continues to occur mainly in the lungs. The technique is labor intensive, requires capital equipment, and runs at high cost.

The intravascular oxygenator is an intracorporeal gas-exchange device placed in the vena cava. It is constructed with polypropylene hollow fibers coated with ultrathin biocompatible siloxane. All blood-contacting surfaces are also coated with covalently bonded heparin. Oxygen is sucked through the fibers, gas exchange occurs through the membranes, and blood is oxygenated intravenously. Placement and maintenance are relatively simple and inexpensive. Because of its relatively small surface area, its capacity is only a third to half of the gas exchange necessary to maintain aerobic metabolism.

Thus, extracorporeal membrane oxygenation is an acceptable technique in the management of neonates with respiratory distress syndrome. In adults, all three techniques are still experimental but have promise. The development of a totally artificial lung remains some time away.

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Bronchiolitis Obliterans Organizing Pneumonia

THE TERM bronchiolitis obliterans organizing pneumonia (BOOP) was coined in 1985 to describe a lung disease characterized histologically by the presence of intraluminal fibroblastic proliferation. In Europe, BOOP is also known as cryptogenic organizing pneumonitis. It has recently been suggested that the disorder be renamed as cryptogenic intramural fibrosis of distal air spaces.

Bronchiolitis obliterans organizing pneumonia is divided into primary or idiopathic and secondary. The secondary BOOP may occur in association with certain infections—with *Legionella, Mycoplasma,* or *Adenovirus* species—the inhalation of toxic gases (nitrogen dioxide), graft-versus-host disease in bone marrow and heart-lung transplant recipients, and collagen vascular diseases. It is, however, the idiopathic or primary BOOP that enters in the differential diagnosis of diffuse interstitial lung disease.

Because of certain common clinical and physiologic abnormalities, BOOP is often misdiagnosed as idiopathic pulmonary fibrosis, sarcoidosis, pneumoconiosis, hypersensitivity pneumonitis, or chronic eosinophilic pneumonia. It is important that BOOP, because of its benign course and favorable response to corticosteroids, is not overlooked or misdiagnosed.

Idiopathic BOOP occurs mainly in adults, with a peak incidence in the sixth decade; women and men are affected equally. Most patients have a subacute illness with cough, dyspnea, fever, and fatigue of a few weeks' duration. The patient's sedimentation rate is often elevated. Although auscultation may reveal rales, in a third of patients the results of a pulmonary examination are normal. Hypoxemia occurs in almost all patients. Lung volumes are reduced, but airway obstruction is not a feature. Diffusing capacity is impaired. Chest roentgenograms show bilateral patchy airspace densities, commonly in peripheral areas, and many other radiographic patterns have also been reported. Honeycombing is rare. The conventional and high-resolution computed tomographic scan findings are nonspecific, but these new techniques are helpful in distinguishing BOOP from idiopathic pulmonary fibrosis and granulomatous lung disease. On histologic examination, the lungs display immature-appearing plugs in the respiratory bronchioles, alveolar ducts, and peribronchial alveolar spaces. The alveolar spaces also contain foamy cells reflecting the proximal airway obstruction. Alveolar septa are thickened and contain mononuclear cell infiltrate. The presence of intraluminal plugs of fibroblasts, however, distinguishes BOOP not only from idiopathic pulmonary fibrosis but also from other interstitial lung disorders.

When should a clinician think about a diagnosis of bronchiolitis obliterans organizing pneumonia? Internists and pulmonologists should consider including BOOP in the differential diagnosis of a subacute interstitial pneumonia, particularly when the patient has influenza-like features with cough, dyspnea, fever, malaise, and weight loss. A poor or unsatisfactory response to antibiotics is another feature favoring this diagnosis. A good transbronchial lung biopsy specimen in conjunction with a strongly suggestive clinical history and examination is in many cases adequate to establish the diagnosis. An open-lung biopsy is needed when a transbronchial biopsy fails to establish the diagnosis. This pneumonia has an excellent prognosis. It responds well to corticosteroids; almost two thirds of the patients in one study improved with the use of corticosteroids. Fewer than 5% of patients die of respiratory failure.

Idiopathic bronchiolitis obliterans organizing pneumonia was recently added to the long list of interstitial disorders. The disease has a benign course with an excellent response to corticosteroids, but we remain ignorant of its cause.

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Advances in Pulmonary Biopsy Techniques

IN THE PAST DECADE, refinements in transthoracic and transbronchial fine-needle aspiration (FNA) techniques, the introduction of thoracoscopic biopsies, and the improvement in lesion imaging and specimen processing have led to a continued decline in the need for open lung biopsies.

The main indications now for percutaneous transthoracic FNA are the biopsy of pulmonary nodules and aspiration of infectious lesions. The diagnostic yield of conventional transbronchial forceps biopsy diminishes with the size of the lesion, whether infectious or neoplastic, so that lesions less than 2 cm to 3 cm are best approached by FNA. In immunocompromised patients, in whom early diagnosis is paramount, small subsegmental and peripheral lesions should undergo FNA under computed tomographic or fluoroscopic guidance because a positive result provides both a diagnosis and confirmation of invasion for otherwise potentially saprophytic organisms like fungi.

Transbronchial FNA by flexible bronchoscopy has the advantage of a lower risk of pneumothorax than percutaneous methods. Its 50% yield in peripheral lesions supplements conventional transbronchial forceps biopsy, washing, and brushing, so that using them together increases the overall yield to about 70%. Compared with transbronchial forceps biopsy, transbronchial FNA is a better technique for metastatic lesions because these tend not to be peribronchial in distribution and hence require deeper biopsies. In addition, about 50% to 60% of malignant mediastinal lymph nodes in paratracheal, subcranial, and aorticopulmonary sites can be sampled with transbronchial FNA guided by computed tomographic images. When successful in the evaluation of lung cancer, this method provides both a cytologic diagnosis and staging, without the need for mediastinoscopy. Because transbronchial FNA has only moderate sensitivity, a negative result does not rule out malignant adenopathy, and it should be noted that the method provides no information about whether disease has spread through the involved node's capsule, a known factor in prognostication. Other uses of transbronchial FNA include the biopsy of extrabronchial compressive lesions and superficially necrotic tumors that require deeper biopsies.

Newer molecular biology and immunohistologic tools have partially eliminated the need for the larger biopsies obtainable only by thoracotomy. Immunohistologic methods using antibodies directed against cell surface antigens can usually separate, for example, reactive lymphocytosis from lymphoma. Gene rearrangement techniques are so sensitive that even cytologic specimens obtained by bronchoalveolar lavage may be adequate for diagnosing certain lymphomas. A polymerase chain reaction assay for *Mycobacterium tuberculosis* holds similar promise for very small or even expectorated specimens in tuberculosis.

When large pleural or parenchymal specimens are required, diagnostic thoracoscopy is now an option. Under general anesthesia, a double-lumen tube is placed to permit collapse of the lung. A rigid thoracoscope is inserted by trocar for plain or video viewing. An operating probe or second thoracoscope, which can incorporate the use of therapeutic carbon dioxide or neodymium-yttrium-aluminum-garnet lasers, is positioned separately to permit wedge excisional biopsy or even segmentectomy. In pleural diseases, thoracoscopy has proved invaluable in diagnosis, and in appropriate cases, therapeutic pleural debridement and even ablation of pleural blebs can be accomplished using these techniques.

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Lung Transplantation

HUMAN LUNG transplantation actually predated heart transplantation, beginning with a single-lung transplant done in 1963. Over the next 15 years, about 44 single-lung transplants were attempted worldwide. The results were uniformly dismal, however, and the procedure was abandoned. Studies of animals suggested that en bloc transplantation of the heart and both lungs provided better vasculature to the tracheobronchial tree, leading to the first successful human heart-lung transplant at Stanford University Medical Center in 1981. This procedure is successful for combined cardiopulmonary disease, particularly congenital heart disease and right ventricular failure associated with pulmonary hypertension. Combined heart-lung blocks are in limited supply, however, stimulating efforts to use lung-only grafts.

Single-lung transplantation was successfully reintroduced in 1983. Major principles advocated were selecting recipients with fibrotic disease only; wrapping the bronchial anastomosis with omentum; not giving preoperative corticosteroids; and avoiding administering maintenance corticosteroids in the early postoperative period. Over the past five years the original principles have been progressively modified: Single-lung transplantation is appropriate for patients with fibrotic disease, emphysema, and perhaps pulmonary hypertension; omental wrapping of the bronchial anastomosis is not required; patients may be successfully transplanted while receiving low dosages of corticosteroids; and instituting corticosteroid therapy immediately following transplantation may be acceptable.

Double-lung transplantation was introduced in 1986. The original procedure involved a low tracheal anastomosis and was technically flawed, with a high rate of tracheal dehiscence. It has now been replaced with bilateral bronchial anastomoses with improved results.

The results of lung and heart-lung transplantation continue to improve with one- and five-year survival rates approaching 75% and 50%, respectively. Candidates for transplantation should have a life expectancy of less than 2 to 3 years without transplantation and be otherwise healthy. Most programs set age limits for transplantation, such as age 60 for single lung, age 50 for double lung, and age 45 for heart-lung transplantation. Rejection monitoring requires frequent assessment of pulmonary function along with bronchoscopy and transbronchial biopsy. The long-term immunosuppression regimen consists of cyclosporine, azathioprine, and prednisone.

Long-term immunosuppression places transplant patients at risk for various unusual infections. In addition, oblitera-

tive bronchiolitis, possibly a manifestation of chronic lung allograft rejection, develops in some recipients and is the major cause of late graft failure. Frequent monitoring of pulmonary function and transbronchial biopsy may allow early detection of this process, but obliterative bronchiolitis progresses inexorably once it is established, despite augmentation of the immunosuppressive regimen.

The major limitation of lung or heart-lung transplantation continues to be an insufficient number of suitable donors, inequities in transplantation funding, and late graft failure from obliterative bronchiolitis. Nonetheless, lung and heart-lung transplantation have become accepted therapeutic options for many patients with heretofore fatal pulmonary disorders.

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Monoclonal Therapy for Bacteremia and Sepsis

GRAM-NEGATIVE BACTEREMIA occurs in 300,000 to 500,000 patients each year. The mortality ranges from 10% to 80% and is highly dependent on a patient's underlying condition and concurrent disease processes. Gram-negative bacteremia is associated with organ failure, which increases mortality, especially if more than one organ is affected. Studies have been done that predict in which septic patient organ failure will develop and, therefore, who will have the highest morbidity and mortality. These predictors have not yet been used clinically, however.

Antiendotoxin antibodies have been used to treat bacteremic patients and patients who appear "septic" despite negative blood cultures. The infusion of endotoxin recapitulates a sepsis-like illness in animals; endotoxin levels are not always detectable in patients with sepsis or even in those with bacteremia, however. Nonetheless, the infusion of polyclonal antiserum to lipid A in patients with gram-negative bacteremia can reduce mortality from 39% to 22%. Patients in septic shock also have had a reduction in mortality, but patients with septic neutropenia do not appear to benefit. The antiserum has never been marketed because of lot-to-lot variation and concern regarding blood products.

Two monoclonal antibodies against endotoxin have recently been developed: HA-1A is a "humanized" immunoglobulin M (IgM) antibody, and E5 is a murine IgM antibody. In clinical studies, the HA-1A was found not to reduce morbidity and mortality in patients with bacteremia or sepsis. In a subset of 200 patients with gram-negative bacteremia with or without shock, mortality was reduced, and there was a trend for a decrease in organ failure in patients with bacteremia treated with the antibody. More patients in the placebo group had renal failure and hepatic failure and had *Pseudomonas aeruginosa* infections, however, leaving some question as to whether the treatment and placebo groups were comparable.

In a study of patients treated with E5, mortality was not reduced, but in a subset of patients who had gram-negative bacteremia but who were not hypotensive, mortality was reduced and there was a trend for less organ failure. A second trial used E5 to treat normotensive septic patients who, conversely, did not show a reduction in mortality. There did seem to be a benefit to the patients who received E5 in terms of a resolution of organ failure, however.

These therapies are expensive. Independent investigators estimated a cost of $24,100 per year of life saved with optimal drug use. They suggested a worst-case scenario, however, of a cost of $1,227,600 per year of life saved. A prudent suggestion would be to await further studies of these agents in selected bacteremic patients, including neutropenic and other immunosuppressed patients, to see if these agents are efficacious in all patients with bacteremia. Also, a comparison study of the two antibodies would clarify some of these issues. Other costly agents will be available shortly, such as antitumor necrosis factor and interleukin receptor antagonists; physicians must be critical of the cost-benefit of these drugs for a condition that has an extremely variable prognosis.

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Conventional Treatment of Cystic Fibrosis

TWENTY YEARS AGO cystic fibrosis meant death by age 7; today the median survival age is 28. This remarkable progress has been accomplished through nutritional support, tracheobronchial care, and multidisciplinary therapy.

Nutritional support is focused on oral ingestion of pancreatic enzymes, high food intake, and vitamin and mineral supplements, particularly the lipid-soluble vitamins A, E, K, and sometimes D. The need for lipid-soluble vitamins is assessed directly by the measurement of vitamin A and vitamin E levels and indirectly by the measurement of prothrombin time and serum calcium levels for vitamins K and D. Acid-resistant pancreatic enzymes have contributed substantially to improved survival rates. The acid resistance allows the enzymes to pass undigested through the stomach into the duodenum. Food requirements for patients with cystic fibrosis can be 20% to 50% higher than normal for at least two recognizable reasons: Patients with cystic fibrosis have some malabsorption despite enzyme replacement, and their metabolic rate is high, probably because of bronchial inflammation and the increased work of breathing. Patients with advanced lung disease may have poor appetites. The use of a gastrostomy tube is gaining acceptance because nutrition status and longevity are correlated.

Tracheobronchial care is less well defined but generally consists of the use of inhaled and oral bronchodilators, antibiotics, and clearing mucus by postural drainage and percussion, sometimes augmented with mucolytics. An active exercise program is also useful. These elements are based on clinical experience and common sense but lack vigorous scientific validation, except that patients are living longer.

Antibiotics are used liberally in these patients. Increased

sputum production, decreased appetite, and shortness of breath are enough to indicate a need for antibiotic therapy. Fever, leukocytosis, or a new infiltrate on a chest roentgenogram are even more imperative signals. Sedimentation rate and quantitative C reactive protein, measures of acute-phase reactants, are used by some as additional indicators for administering antibiotics. The typical antibiotic course is long—14 to 21 days. Some patients use antibiotics nearly continuously, sometimes administered by aerosol in those with substantial secretions. Antibiotic use is guided by sputum cultures: *Haemophilus influenzae*, *Staphylococcus aureus*, and, later in life, *Pseudomonas aeruginosa* are the usual pathogens. Many antibiotics have an accelerated half-life in these patients, and dosage has to be adjusted accordingly.

Postural drainage and percussion preceded by an inhaled β-agonist is traditionally recommended twice a day. Lung transplantation, with a 50% survival at 2 years, is considered for patients with end-stage lung disease.

Cystic fibrosis is a complex disease with numerous medical, psychiatric, and social consequences. For patients and their families, it means a lifetime of adjustments. Patients can be managed by individual physicians but should also be registered with a cystic fibrosis center for consultation and provision of otherwise unavailable services. Such centers are identified by the National Cystic Foundation (1-800-FIGHT CF) and in California by the State Genetically Handicapped Persons Program (916-654-0503) and California Children's Service (916-654-0499).

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Aerosolized Bronchodilators

BECAUSE OF DIRECT DELIVERY to the site of action, inhaled bronchodilators are rapidly effective even in small quantities and, hence, cause a minimum of systemic side effects. Whether bronchodilators are inhaled through a nebulizer, through a metered-dose inhaler (MDI) with or without spacer, or through a dry powder inhaler (DPI), only about 10% to 20% of the inhaled drug traverses the major barrier of the upper airways and is available for deposition on potentially beneficial spots in lower airways. When selecting a form of aerosol administration, physicians should weigh the advantages and disadvantages of each type.

Nebulizers are expensive, labor intensive, and inconvenient compared with MDIs and DPIs. Unusual bronchodilators such as the anticholinergic glycopyrrolate can be delivered only by nebulizer. The waste in nebulizers is in the loss of drug in tubing and apparatus. Though nebulizers have been widely used for years, adjustment of the major elements of operation including fill volume, operating pressure and flow, and length of time of nebulization is not well established; hence, nebulizers are frequently not used well. Though nebulizers are as efficient as MDIs, amounts of medication used and delivered are much greater, and, hence, the possibility of side effects from overdosage is much greater.

Because of their convenience of size and the availability of most major bronchodilators, MDIs are widely used. Appropriate technique requires the coordination of canister activation with slow inhalation and breath-holding. While most patients can learn this technique, some will require aids such as spacers. Because spacers are less convenient, alternatives such as breath-actuated devices may be useful.

Though some drugs are available in the dry powder inhaler format, its use is not common. Within several years, when freon propellants are no longer available, DPIs probably will be used more frequently. A possible advantage of the DPI is that it delivers a drug as efficiently as a nebulizer or MDI without requiring coordination between activation and inhalation. New DPIs deliver several doses of a drug without the inconvenience of reloading.

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Screening for Obstructive Sleep Apnea Using Pulse Oximetry

RECENT RESEARCH has indicated that obstructive sleep apnea is much more common than generally appreciated. The reported prevalence is 1% to 5% in unselected populations and even greater in selected populations such as habitual snorers (30% to 50%). It is also serious, with an 8- to 11-year mortality of about 30%, affecting individuals through associated disease and society through sleep disruption and its effects on job performance and driving. At present, the recommended diagnostic tool is nocturnal polysomnography, but the expense, inconvenience, and lack of general availability of this test have deprived patients of the benefit of treatment.

The appropriate screening tool for obstructive sleep apnea remains to be defined. A patient's history may be highly suggestive, but only that, in 60% to 70%—snoring, observed apneas, and obesity, particularly truncal, are the most predictive. Examination will rarely be specific, even the direct observation of sleep. Pulmonary function tests are also not helpful; the sawtooth pattern of the flow-volume curve has been discredited as a marker. The non-neurophysiologic elements of the polysomnogram have also been suggested, but the absence of airflow, the sine qua non of obstructive sleep apnea, is difficult to record easily. The electrocardiogram often shows a characteristic, repetitive tachycardia-bradycardia, a consequence of the repetitive apneas, but the presence of an autonomic neuropathy will mask this.

Pulse oximetry has been shown to be highly specific (100%) but, using current accepted criteria for abnormal desaturations (less than or equal to 4%), is not sufficiently sensitive (60% to 70%). Two recent studies have highlighted this. At present, therefore, the screening of populations by visual analysis of pulse oximetry traces alone will lead to an underestimate of the prevalence of obstructive sleep apnea. In selected populations where clinical suspicion exists—sleepy snorers, for example—a negative or indeterminate pulse oximetry trace may not obviate the need for further study. Because oximetry is so specific, however, a positive study may allow the physician to introduce therapy such as nasal continuous airway pressure, with an abolition of symptoms being the criterion for adequate treatment.

An additional confounding problem is the presence of the periodic limb movement disorder in some patients, which can independently cause substantial sleep deprivation. The prevalence increases with age—5% at 30 to 50 years of age and 44% at 65 and older—and has been found in 5% to 18% of patients suspected of having obstructive sleep apnea.

Because of the lack of sensitivity of oximetry and the coexistence of other disorders causing sleep disruption, screening for obstructive sleep apnea using only oximetry will not obviate the need for further study in a symptomatic patient. The electroencephalogram may not be essential, but, in addition to oximetry and clinical assessment, a measurement of respiratory activity and of leg movements is probably needed in the evaluation for this disorder as further refinement of the interpretation of the oximetry tracing is undertaken.

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Alerts, Notices, and Case Reports

Long-standing Latent Idiopathic Hypoparathyroidism Discovered During Concurrent Central Nervous System Disease

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HYPOPARATHYROIDISM is a metabolic disorder that manifests as hypocalcemia and hyperphosphatemia due to the deficiency of parathyroid hormone (PTH) secretion.[1] Most commonly, hypoparathyroidism is secondary to neck operations, especially thyroidectomy. It can also be due to congenital defects such as the DiGeorge syndrome; infiltrative diseases such as carcinomatosis or amyloidosis; or inherited by autosomal dominant,[2] autosomal recessive,[3] or X-linked mechanisms.[4-6] The idiopathic form is defined as hypoparathyroidism not occurring after a surgical procedure or any other well-defined cause; it may be a component of an autoimmune polyglandular failure syndrome or an isolated disorder. When isolated idiopathic hypoparathyroidism occurs in an adult, it is usually a rare, sporadic event[1] that commonly has been present for a long time before diagnosis.

Clinically, hypoparathyroidism presents with symptoms related to hypocalcemia such as tetany, seizures, osseous abnormalities, or psychiatric abnormalities. Occasionally it is completely asymptomatic. We report two cases of long-standing asymptomatic idiopathic hypoparathyroidism that became symptomatic with the onset of concomitant central nervous system (CNS) processes.

Report of Cases

Case 1

The patient, a 27-year-old Filipino woman with no history of medical problems, had had myalgias, fever, and headaches for several days before admission. On the day of admission, her husband found her at home in a fetal position, unresponsive but in no acute distress, and she was taken to the University of Nevada Medical Center (Las Vegas) for evaluation. Family members said that she had had normal physical development and normal mental function before this admission. She ate a traditional Filipino diet and did not drink milk daily. On physical examination she was normally developed and had a temperature of 40°C (104°F) and tachycardia but no respiratory compromise. There were no skin, nail, or digit abnormalities. An ocular examination revealed no cataracts, and dentition was normal except for the absence of two incisors due to trauma as a child. There was moderate nuchal rigidity and globally diminished muscle tone and deep tendon reflexes. Trousseau's sign was present but Chvostek's sign was absent. Babinski's signs were absent. The results of the examination were otherwise normal.

Laboratory studies disclosed the following values: leukocytes, 14×10^9 per liter (14,000 per μl), with a normal differential count, and hematocrit 0.45 (45%); serum sodium, potassium, creatinine, and alkaline phosphatase, within normal limits; calcium, 1.40 mmol per liter (5.6 mg per dl; normal, 2.17 to 2.65 mmol per liter); phosphorus, 1.45 mmol per liter (4.5 mg per dl; normal, 0.80 to 1.55 mmol per liter); albumin, 41 grams per liter (4.1 grams per dl; normal, 33 to 50 grams per liter); and magnesium, 0.70 mmol per liter (1.7 mg per dl; normal, 0.70 to 1.11 mmol per liter). Computed tomography (CT) of the head showed extensive calcification in the basal ganglia and posterior fossa but was otherwise unremarkable (Figure 1). A cerebrospinal fluid examination revealed a leukocyte count of 265×10^6 per liter (265 per μl), with 0.90 mononuclear cells and 0.10 polymorphonuclear cells; protein concentration, 1.98 grams per liter (198 mg per dl); and glucose, 2.2 mmol per liter (40 mg per dl) with a concurrent serum glucose level of 7.7 mmol per liter (139 mg per dl). Cultures of cerebrospinal fluid, including for mycobacteria, were negative.

Figure 1.—A computed tomographic scan of the head without intravenous contrast enhancement shows extensive intracranial calcification mainly within the basal ganglia **(arrow).**

The patient subsequently had tonic-clonic seizures. Treatment was instituted with parenteral antibacterials, acyclovir, phenytoin, and calcium gluconate. Her stupor abated once serum calcium levels rose above 1.62 mmol per liter (6.5 mg per dl), at which point she gave appropriate responses to simple questions. Therapy with oral elemental calcium, 1,500 mg per day, and ergocalciferol, 50,000 IU per day, was begun. The patient subsequently aspirated oral nutritional tube feedings and required several days of me-

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ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
PTH = parathyroid hormone

chanical ventilation due to respiratory failure. After extubation her course was complicated by a transient episode of hyponatremia—a serum sodium level of 118 mmol per liter (118 mEq per liter; normal, 135 to 153) with a concurrent urine osmolality of 507 mmol per kg (507 mOsm per kg) of water. Thyroid and adrenal function was normal, and the hyponatremia corrected with free water restriction. The patient was treated empirically with a ten-day course of acyclovir. She showed steady improvement in mental function over the three weeks of her hospital stay. The serum intact PTH level was measured at 0.98 pmol per liter (4 pg per ml; normal, 2.44 to 15.86 pmol per liter), and the 25-hydroxycholecalciferol level was 88 nmol per liter (35 ng per ml; normal, 22 to 130 nmol per liter) in serum specimens drawn before calcium and vitamin D therapy. The final diagnosis was viral meningoencephalitis with hypoparathyroidism-induced hypocalcemia exacerbating her CNS symptoms. She was discharged with normal neurologic function.

Case 2

The patient, a 35-year-old man, was struck by an automobile while walking near the street. He did not lose consciousness and was transported to the University Medical Center for emergency evaluation. Family members reported that the patient was previously healthy and took no medications. A physical examination revealed a large scalp laceration but no other serious trauma. There were no skin, nail, or digit abnormalities. No cataracts were noted. The patient responded to voice by opening his eyes and withdrew from painful stimuli. Deep tendon reflexes were globally decreased. The results of the examination were otherwise normal.

The patient's complete blood count and serum electrolytes were within normal limits. A chest x-ray film was normal. A CT scan of the head revealed intraventricular hemorrhage and extensive parenchymal calcification in the basal ganglia and posterior fossa (Figure 2). The patient remained in a stupor and had generalized tonic-clonic seizure activity that lessened after intravenous phenytoin therapy. He then underwent a ventriculoperitoneal shunt placement for decompression of intraventricular bleeding. The patient continued to have a substantially depressed mental state after the shunt placement. Biochemical screening done three days after admission revealed the following values: serum calcium, 1.35 mmol per liter (5.4 mg per dl); phosphorus, 1.81 mmol per liter (5.6 mg per dl); albumin, 40 grams per liter (4.0 grams per dl); and magnesium, 0.58 mmol per liter (1.4 mg per dl). The patient was given intermittent parenteral calcium gluconate infusions, elemental calcium at a dose of 1.0 grams daily, and calcitriol, 1.0 μg daily, with improvement of his serum calcium level to greater than 1.75 mmol per liter (7.0 mg per dl). His mental state improved after several days of therapy, and he was transferred to a rehabilitation service. Blood specimens drawn before calcium and vitamin D therapy revealed the serum intact PTH level to be less than 0.73 pmol per liter (3 pg per ml), and a serum 25-hydroxycholecalciferol level was 132 nmol per liter (53 ng per dl).

Discussion

The differential diagnosis of hypocalcemia with normal or elevated serum phosphorus levels in critically ill patients includes hypoalbuminemia, acute or chronic renal failure, phosphate excess, vitamin D deficiency, or PTH deficiency due to hypomagnesemia. In rare cases, a patient presents with previously unrecognized idiopathic hypoparathyroidism. The prevalence of unrecognized hypoparathyroidism has been estimated to be from 0.006% to 0.02% of the population as determined by routine biochemical screening.[7,8] Basal ganglia calcifications can be noted in 0.7% of routine CT scans of the head but is usually not due to idiopathic hypoparathyroidism.[9] When basal ganglia calcification is seen in a patient with hypocalcemia, however, it is strongly suggestive of long-standing hypoparathyroidism.

The key to the diagnosis of idiopathic hypoparathyroidism is the exclusion of other clinical disorders that may also present with hypocalcemia. Hypomagnesemia can be easily diagnosed by biochemical screening. Low serum magnesium levels aggravate the degree of hypocalcemia by both decreasing PTH secretion and producing end-organ resistance to PTH at the bone and kidneys. Of note is that both of the patients had low or low-normal magnesium levels, which may have exacerbated their hypocalcemia. Other causes of hypocalcemia can be readily excluded except for vitamin D deficiency and pseudohypoparathyroidism, which can be diagnosed with the aid of serum measurements for 25-hydroxycholecalciferol and intact PTH, respectively. Patients with pseudohypoparathyroidism generally have an elevated PTH level due to renal hyporesponsiveness to PTH. This syndrome often has the phenotypic changes of Albright's hereditary osteodystrophy with short fourth metacarpals and

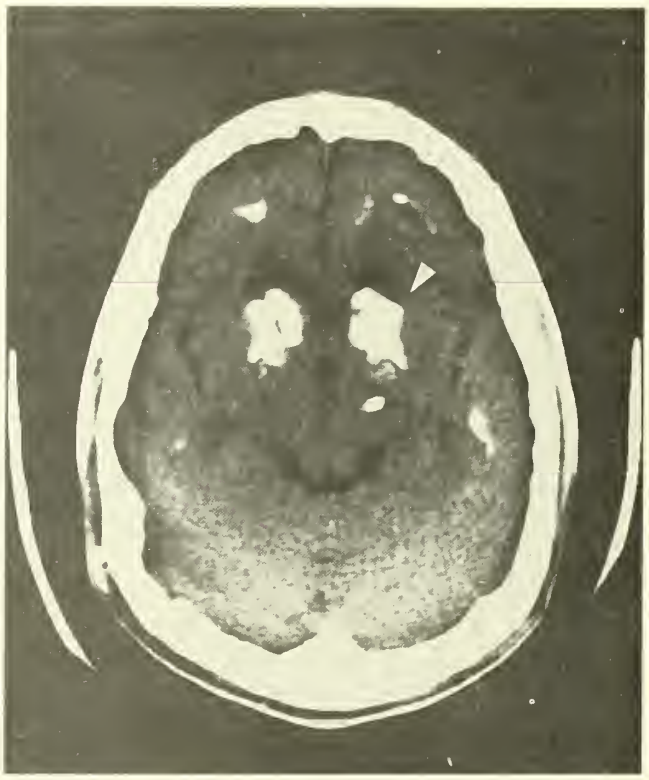

Figure 2.—A computed tomographic scan of the head without intravenous contrast enhancement shows intraventricular hemorrhage and extensive parenchymal calcification in the basal ganglia (arrow) and posterior fossa.

a family history of similar disorders. Another disorder that must be excluded is the autoimmune polyglandular syndrome type I, which comprises hypoparathyroidism, Addison's disease, and mucocutaneous candidiasis, at least two of which must be present to make the diagnosis. Once these syndromes are excluded and a serum intact PTH level is very low with concurrent hypocalcemia, a diagnosis of idiopathic hypoparathyroidism can be made. This disorder can be caused by an isolated autoimmune destruction of parathyroid tissue, which is a possible cause of the hypoparathyroidism in both of the cases presented. If there is no PTH activity, the serum calcium level will be near 1.25 mmol per liter (5.0 mg per dl), representing the solubility of bone mineral in the serum.[1]

Idiopathic hypoparathyroidism is rare, and it is not uncommon for patients to go for long periods of time without symptoms.[1,10] These two patients have had this disorder for several years as both had extensive intracranial calcifications. It can also cause notable ligamentous and soft tissue calcification.[11] Before the common use of CT scanning, studies of patients who had undergone surgical parathyroidectomy have shown that 17 years elapse before radiographic evidence of intracranial calcifications.[1] Computed tomography is more sensitive than routine radiography in detecting intracranial calcifications.[9] Because of the extensive intracranial calcifications in the two cases presented, however, both patients are likely to have had hypocalcemia for more than 17 years.

Chronic hypocalcemia can present as seizures, cognitive or psychiatric alterations in CNS function, or extrapyramidal signs in the neonate to the elderly populations.[10,12-15] These symptoms can also wax and wane in older patients.[16] It is therefore important to evaluate serum calcium levels in all patients who present with new CNS symptoms. As seen in the two cases presented here, however, even those persons with asymptomatic hypoparathyroidism are likely to have a subclinical alteration in CNS function, and a concurrent CNS process can produce serious symptoms such as seizures, stupor, or coma. In both of the cases presented, the stuporous state resolved considerably with calcium repletion. Adaptation to chronic hypocalcemia can be accomplished by increasing the dietary intake of calcium, which was not historically present in these two patients. Unfortunately, calcium supplementation does not always prevent further intracerebral calcification or a progression of CNS dysfunction.[14]

In summary, idiopathic hypoparathyroidism is considered a rare disease that can present with a variety of neurologic or psychiatric symptoms or be clinically silent. With the widespread use of multichannel biochemical screening tests and CT scans of the head, asymptomatic hypocalcemia and intracranial calcification may be recognized more commonly in clinical practice. In these cases, physicians must consider the possibility of parathyroid hormone abnormalities.

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Cerebral Infarction as a Remote Complication of Childhood *Haemophilus influenzae* Meningitis

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STROKE IS RARE in children, and when it does occur it is associated with different causes than in adults. One of the most common causes of acquired cerebrovascular disease in children is central nervous system infection. For instance, in some selective studies, cerebral infarction developed in as many as 27% of children with complicated bacterial meningitis during their hospital stay.[1,2] The pathophysiology of infarction in these patients is not clear, but it is thought to involve, singly or in combination, vasculitis,[1-4] coagulopathy, or vasospasm.[4-6] Vasculitis when it occurs may then have long-term structural consequences for blood flow in the brain.[4,7] In this report we present a case of cerebral infarction that occurred six years after *Haemophilus influenzae* meningitis and that we think represents a delayed consequence of meningitis-associated arteriopathy. To our knowledge, delayed infarction from *H influenzae* meningitis has not been reported to date.

Report of a Case

The patient, a 6-year 10-month-old boy, presented to the Primary Children's Medical Center Emergency Department (Salt Lake City, Utah) because in the previous 12 hours he

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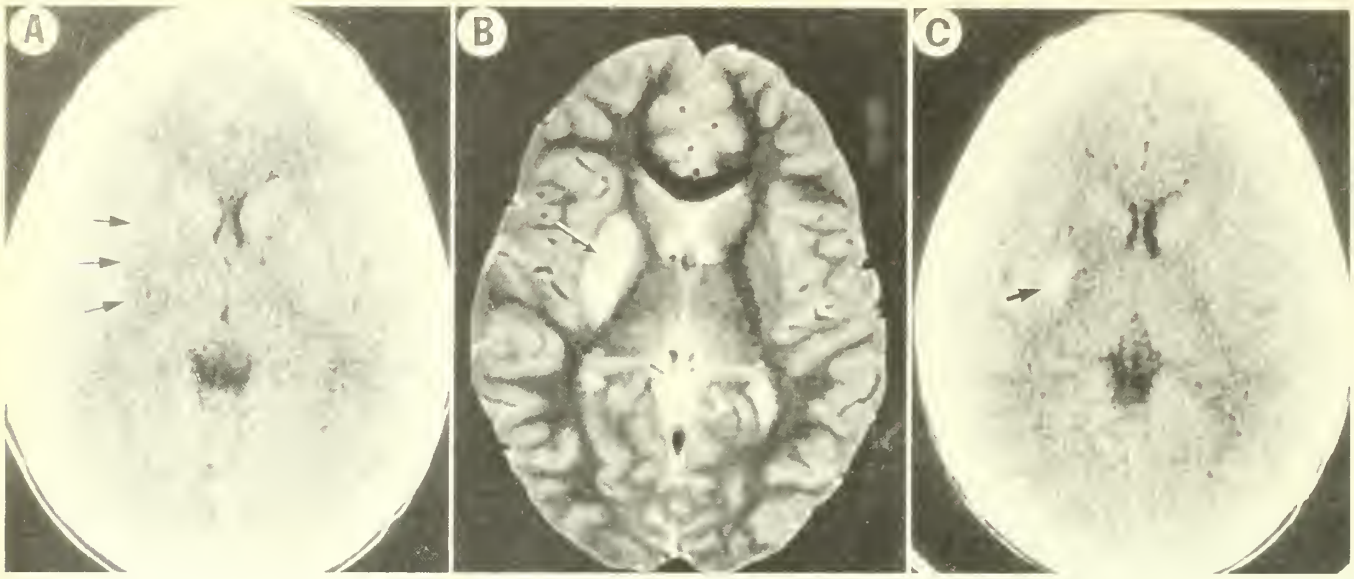

Figure 1.—**A,** An enhanced computed tomographic (CT) scan of the brain done shortly after admission shows a poorly defined area of hypodensity **(arrows)** in the vicinity of the right putamen and globus pallidus with a slight degree of mass effect. **B,** A magnetic resonance image taken 3 days after admission shows notably increased signal on T2-weighted images **(arrow),** confirming the presence of a right basal ganglia infarction. **C,** After neurologic deterioration on the 5th hospital day, a second (unenhanced) CT scan showed a small hemorrhage in the right basal ganglia **(arrow).**

had had transient episodes of left-sided weakness lasting about 2 to 40 minutes each, with complete resolution between episodes. The patient had been previously healthy except for a bout of *H influenzae* type B meningitis at the age of 4½ months. On the day of admission for meningitis, the patient was noted to have a bulging fontanelle, vomiting, listlessness, and nuchal rigidity, with a maximum temperature of 39.6°C. Cerebrospinal fluid (CSF) analysis showed 9,258 leukocytes $\times 10^6$ per liter with 0.66 polymorphonuclear leukocytes, 0.22 band forms, and 0.12 lymphocytes. There were 552 erythrocytes $\times 10^6$ per liter. A CSF protein level was 3.26 grams per liter (326 mg per dl), and the glucose concentration was 1.1 mmol per liter (20 mg per dl). A regimen of ampicillin and chloramphenicol was started. Cultures of blood and CSF grew *H influenzae* type B. On the evening of admission, the patient was noted to be in status epilepticus with tonic seizures, compromising his respiratory effort. He was intubated, given phenobarbital, and transferred to the intensive care unit where he stayed overnight. He was then transferred back to the floor, and the rest of his stay in the hospital (about two weeks) was uneventful. Neither an electroencephalogram nor a computed tomographic brain scan was obtained during this admission. The patient was described as having no appreciable neurologic deficit at the time of discharge. No further seizures occurred after discontinuation of the anticonvulsant several months later, and the only possible neurologic deficit was a mild speech delay, accompanied by an articulation disorder that may not have been related to his meningitis. By parental report, developmental milestones were otherwise achieved early or on time. After this illness, the patient had only minor colds until the occurrence of episodes of left hemiparesis. There was no family history or personal history of clotting disorders. The paternal grandmother was known to have migraines.

Before and during the admission process, the patient had four episodes of left-sided weakness. The first, lasting ten minutes, occurred while he was sitting quietly. During this episode his left face, arm, and leg became weak and speech was slurred, although consciousness was not impaired. A second episode, which also lasted ten minutes, occurred six hours later and was similar except that it was accompanied by a headache that could not be localized to any region of the head. No nausea or vomiting occurred, and again the patient remained fully alert. Some three hours later, on arrival at the emergency department, the patient sustained a similar episode lasting 40 minutes, followed by a final episode two hours later, lasting 2 minutes. In this episode his arm was profoundly weak and flaccid, and he could not stand well due to weakness of the left leg. Speech remained unaffected during this last episode.

On physical examination he was alert and oriented with an occipitofrontal circumference of 52 cm (50th percentile), weight 25.5 kg (75th percentile), and height 126 cm (75th percentile). The findings of a general physical examination were completely normal. Pulses were strong, symmetric, and without bruits. Between episodes, the patient was noted to have a slight facial droop on the left (central seventh cranial nerve palsy) and mild weakness of both extremities on the left side. A Babinski's sign and ankle clonus could be elicited on the left, and clumsiness of movement was demonstrated with the heel-to-shin maneuver. Hopping and rapid alternating movements were likewise impaired on that side.

Additional studies were done. A computed tomographic scan obtained at presentation (Figure 1-A) showed a vague region of hypodensity involving the right putamen and globus pallidus, accompanied by a minimal mass effect. A magnetic resonance imaging scan (Figure 1-B) confirmed the presence of a right basal ganglia infarction. Cerebral angiography revealed mild stenosis of the M1 segment of the right middle cerebral artery and a pronounced stenosis of the A1 segment of the right anterior cerebral artery (Figure 2). The lenticulostriate branches were more prominent on the ipsilateral side, suggesting a chronic process or "luxury perfusion."

Laboratory investigations did not elucidate any definite cause for these vascular events. A rapid plasma reagin test was nonreactive. An erythrocyte sedimentation rate was 1 mm per hour, cholesterol level was 4.14 mmol per liter (160 mg per dl), and triglycerides were 0.85 mmol per liter (75 mg

per dl). Initial prothrombin and partial thromboplastin times were normal. Screening for homocystinuria was negative. Antithrombin III and protein C levels fell within the normal range. The protein S concentration was slightly diminished (0.58; normal range, 0.66 to 1.12). (This laboratory determination was rechecked months after discharge because it is thought that endogenous anticoagulant levels may be misleading in the acute phase of a vascular illness.[8,9] When rechecked, the protein S value was in the normal range.) Anticardiolipin antibodies and lupus anticoagulant were undetectable. An echocardiogram was normal.

The patient's hospital course was as follows: A regimen of intravenous heparin and oral warfarin sodium was instituted, with a long-term goal of oral anticoagulation. On the second hospital day, he had another episode of left-sided weakness lasting 12 minutes but then remained stable without similar episodes for three days.

At this point, despite an appropriate degree of anticoagulation (prothrombin time 17.2 seconds, partial thromboplastin time 79 seconds), the patient had two more episodes similar in character to previous ones but leaving him with greater residual deficit. A second computed tomographic scan of the brain (Figure 1-C) obtained soon after these episodes showed small hemorrhages in the right globus pallidus and right caudate nucleus with a mild mass effect.

Because of this complication, anticoagulation was discontinued. Over the next few days, his condition improved until he reached the functional level described at the time of his admission. He was then started on aspirin therapy, 160 mg per day, and discharged. A week later his muscle strength had improved somewhat, but tone continued to be increased in his left upper and lower extremities. A Babinski's sign remained on the left, and ankle clonus could be elicited.

No further episodes have occurred since discharge. A follow-up examination two years after his original stroke revealed symmetric muscle strength but continued increased tone on the left side, particularly in the lower extremity, and noticeably impaired gross and fine motor skills on this side.

Discussion

This case is thought to represent a delayed consequence of vasculopathy due to *H influenzae* meningitis, although it is possible that the meningitis and subsequent stroke are coincidental. The proposed mechanism is a meningitis-induced vasculitis leading to a fixed but subclinical stenosis. This was then followed years later by an episode of hypoperfusion by any of several mechanisms (discussed later). The following observations support this contention. First, vascular involvement in childhood meningitis has been demonstrated histologically[10-12] and angiographically.[4,6,13] Second, cerebral infarction is a recognized complication of meningitis during the acute phase of the illness.[1-3,14,15] Third, the vasculopathy accompanying childhood meningitis may be persistent,[4,7] progressive, or both, thereby leading to vessel stenosis.[5,7] The angiographic findings in this child (Figure 2) would be compatible with such long-term effects. Finally, no alterna-

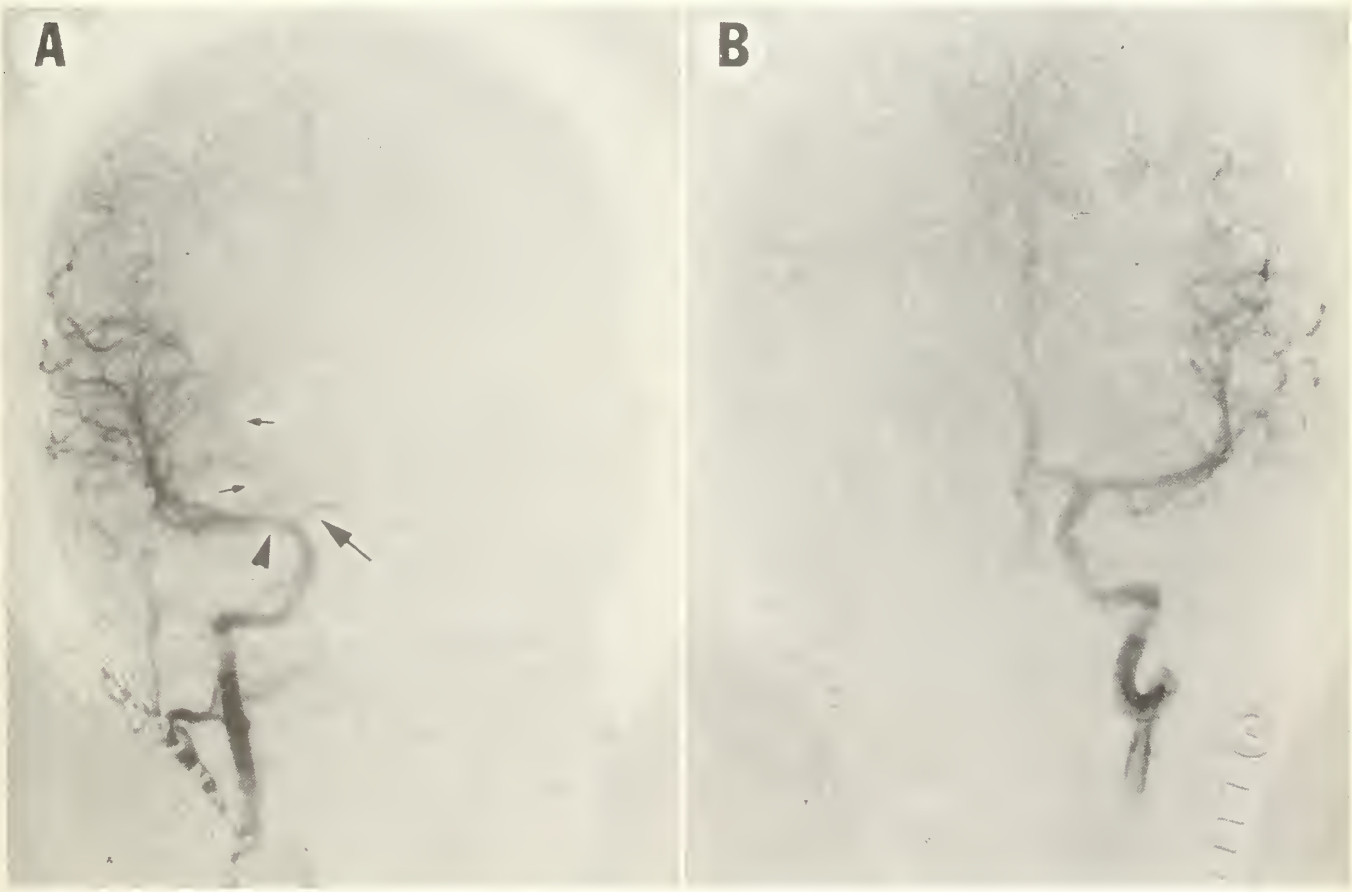

Figure 2.—**A,** An anteroposterior angiogram reveals mild stenosis of the M1 segment of the right middle cerebral artery **(arrowhead)** and a marked attenuation of the A1 segment of the right anterior cerebral artery **(large arrow).** Lenticulostriate arteries were enlarged **(small arrows),** indicating "luxury perfusion" or a chronic process with vascular proliferation. **B,** An anteroposterior view of the left carotid artery is shown for comparison. Note the absence of changes described for the right side.

tive explanation for this boy's cerebral infarction could be found. Specifically, there was no apparent infection or inflammatory response and no evidence for a clotting disorder or source of embolic material.

There are some questions about the degree of involvement of vasospasm versus organic stenosis or occlusion in the vasculopathy of meningitis and whether organic stenosis or occlusion is permanent. For example, two children with angiographic evidence of cerebral arterial stenosis during an acute meningitic illness and with persistent neurologic deficit were later found to have patent—apparently normal—vessels on angiography.[6] Another child, however, with angiographic evidence of pronounced stenosis of both internal carotid arteries was found at autopsy to have thickened carotid arteries with mural vasculitis, involvement of the intima, and "marked" luminal narrowing.[4]

Vasculitis accompanying meningitis is thought to evolve as follows: The intima of cerebral vessels is elevated by polymorphonuclear cell infiltration of the vessel wall, causing luminal narrowing. Long-term effects include the proliferation of connective tissue in the vessel wall with the destruction of smooth muscle fibers, often accompanied by partial or total destruction of the internal elastic lamina, producing a stenotic vessel lumen.[7] Yamashita and co-workers have suggested that the initial damage to the media may in part be due to the intense contractions of smooth muscle fibers that accompany the vasospasm presumed to occur with meningitis.[5] They too propose that the resultant mural thickening may lead to organic stenosis of major cerebral arteries.[5]

It is argued that the patient in this case had vasculitis associated with his early meningitis but that infarction did not occur initially or was insufficient to result in clinically detectable effects. Accompanying vasculitis did, however, lead to fixed, organic stenoses of the right anterior and middle cerebral arteries. This could have predisposed the patient to subsequent distal ischemia by several mechanisms. First and most likely, hypotension or hypovolemia might have produced hypoperfusion and ischemia distal to a fixed stenosis, perhaps from a trivial event such as neck bending or twisting.[16] Second, an intraluminal thrombus could have developed in the stenotic artery due to turbulent or sluggish blood flow. Third, the stenosis might have progressed in this patient, leading to clinical symptoms. In this regard, Rorke has suggested that the stenotic process can occur over a protracted period of time.[7] It is unclear in the present case whether the patient had a fixed stenosis through which flow was later compromised or an evolving stenosis, although because there appears to be no tendency after meningitis for repetitive infarcts, an evolving stenosis is unlikely. Because infarction is often minimal despite marked narrowing of the cerebral vasculature, Rorke suggests that in many cases collateral circulation develops.[7] It is interesting that in the case reported here the right lenticulostriate branches were enlarged on angiography and might represent such collateral circulation. In addition, other vasculopathies such as those associated with cranial irradiation have occurred with delayed cerebral infarction.[17]

In conclusion, the case reported here represents only one of the diverse causes of stroke in children. This is arguably an example of delayed cerebral infarction due to the vasculopathy associated with *H influenzae* meningitis sustained in infancy. Other than that this child was generally quite ill with his meningitis as an infant, as is common, he did not seem to have any particular predisposing factor for infarct. It is also unclear if the *H influenzae* organism causes more vasculitis than others. A prospective or retrospective study to determine the frequency of late vascular events in children following meningitis would be interesting and helpful to sort out these questions. Many such sequelae may now be preventable with the vaccination of infants with the *H influenzae* type B polysaccharide vaccine. This case suggests that inquiring about a history of early infections is important in children with stroke, much as a history of the Kawasaki syndrome is important in childhood myocardial infarction.[18]

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Ehrlichiosis in a Visitor to Virginia

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HUMAN EHRLICHIOSIS has only recently been described in the United States.[1] Of the more than 100 cases reported, almost all have occurred in the Southeast or the South Central states.[2,3] We describe a case in a California resident who almost certainly acquired the disease in Virginia. This case, which as of this date is the first reported from California, illustrates the severity of the illness and the multiple manifestations that can occur, including pneumonitis, meningoencephalitis, hepatitis, hyponatremia, and hematologic abnormalities.

(Armstrong RW: Ehrlichiosis in a visitor to Virginia. West J Med 1992 Aug; 157:182-184)

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Report of a Case

The patient, a previously healthy 63-year-old woman, sustained two insect bites on her left leg on May 10, 1991, while visiting relatives in a rural area in southern Virginia near Appomattox. The bites were noted after she returned from a walk in a wooded area. The bites were presumed by the patient to be from ticks, but the insects were not observed. After she returned to northern California, she had the insidious onset of illness on about May 26 in which headaches, malaise, anorexia, nausea, and mild feverishness developed. The headaches worsened and became incapacitating; they were unrelieved by taking oral analgesics. Nausea progressed to several episodes of vomiting. Temperatures were recorded at 37.8°C to 38.3°C (100°F to 101°F). On June 4, treatment with cephalexin was initiated. A progressive worsening of symptoms, including neck pain, myalgias, abdominal pain, and increased fever, led to hospital admission on June 7.

On admission the patient's temperature was 38.7°C (101.7°F), respirations 28 per minute, pulse 100 beats per minute, and blood pressure 90/50 mm of mercury. The findings of the initial physical examination were described as basically unremarkable except for dehydration. Intravenous fluids and intravenous cefazolin were administered. Overnight her temperature rose to 39.6°C (103.2°F), her blood pressure fell to 84/40 mm of mercury, and her pulse never rose to more than 110 per minute. In the first 16 hours, her urinary output was only 180 ml despite an input of 2,000 ml of intravenous fluids.

The next day the patient was mildly confused and forgetful. She was thirsty and had abdominal and neck pain. Her mucous membranes were dry, her blood pressure fell 20 mm of mercury when she sat up, and there was mild resistance to full neck flexion. Crackles were heard at the lung bases. Her jugular venous pressure was less than 5 cm of water. A cardiac examination showed no abnormalities. Diffuse abdominal tenderness and hypoactive bowel sounds were noted. There were no masses or hepatosplenomegaly. No lymphadenopathy, exanthem, or focal neurologic signs could be found.

Initial laboratory results included the following: leukocyte count, 12.7×10^9 per liter (0.88 segmented neutrophils, 0.05 band forms, 0.03 lymphocytes, 0.04 monocytes); hemoglobin, 126 grams per liter (12.6 grams per dl); hematocrit, 0.36; platelet count, 187×10^9 per liter; glucose, 7.7 mmol per liter (138 mg per dl); blood urea nitrogen, 11.4 mmol per liter (32 mg per dl); creatinine, 97 μmol per liter (1.1 mg per dl); sodium, 124, potassium, 4.4, chloride, 88, and carbon dioxide, 26 mmol per liter; alkaline phosphatase, 233 units per liter (normal 25 to 128); lactate dehydrogenase, 1,910 units per liter (normal 259 to 506); aspartate aminotransferase (formerly SGOT), 93 units per liter (normal, 3 to 26); bilirubin, 23 μmol per liter (1.4 mg per dl); total protein, 63 grams per liter; and albumin, 36 grams per liter. A prothrombin time was normal, and tests for rheumatoid factor and rapid plasma reagin were negative. A urinalysis was normal. Arterial blood gas determinations with the patient breathing room air showed a pH of 7.45, a P_{CO_2} of 4.27 kPa (32 mm of mercury), and a P_{O_2} of 6.8 kPa (51 mm of mercury) (90% saturation). The chest x-ray film showed a faint bibasilar interstitial infiltrate in the lower lung fields; cardiac size and vascular markings were normal. Culture of blood, urine, and stool specimens obtained on admission was subsequently unremarkable.

On the second hospital day, laboratory test results were essentially unchanged. A contrast computed tomographic brain scan was normal. A lumbar puncture had an opening pressure of 180 mm of water; the fluid was clear. The cerebrospinal fluid protein concentration was 1.2 grams per liter (120 mg per dl), glucose was 4.0 mmol per liter (73 mg per dl), the leukocyte count was 80×10^6 per liter (0.76 neutrophils, 0.04 lymphocytes), and an erythrocyte count was 1×10^6 per liter. A Gram's stain, an india ink preparation, and an acid-fast stain were all negative; cultures were later negative for bacteria, fungi, and mycobacteria. Antibiotic therapy was changed to intravenous gentamicin sulfate and ceftriaxone sodium. On the third hospital day, the patient remained febrile. Her blood pressure fell transiently to 60/0 mm of mercury but responded to an increased infusion of saline solution. Her mental obtundation increased. Another cerebrospinal fluid examination showed an increased number of leukocytes to 128×10^6 per liter, the glucose content decreased to 2.4 mmol per liter (44 mg per dl), and the protein level rose to 1.27 grams per liter (127 mg per dl). All stains were again negative for organisms, and cultures were again subsequently negative. The previous antibiotic regimen was discontinued, and a regimen of intravenous doxycycline, 100 mg every 12 hours, was begun.

Within 24 hours of the initiation of the doxycycline therapy, she became afebrile. The severe headache, nausea, and generalized abdominal pain required three days to abate. During the rest of her hospital stay, the lymphopenia was replaced by lymphocytosis and the serum sodium level gradually returned to normal. She was discharged on the sixth hospital day; the regimen of doxycycline was continued orally to complete 14 days of therapy. On the day of discharge, she had a fine tremor of her upper extremities. The tremor, anorexia, and weakness resolved after about four weeks.

Serologic testing done by the Centers for Disease Control (CDC) using indirect fluorescent antibody methods gave the following results: acute-phase serum from the 10th day of illness: Rocky Mountain spotted fever 1:32, typhus less than 1:16, Q fever less than 1:16, *Ehrlichia chaffeensis* 1:32; testing of a convalescent serum specimen (28 days later) showed unchanged values for everything except the *E chaffeensis*, which was 1:512. The CDC also demonstrated bacterial 16S ribosomal RNA gene sequences specific for *E chaffeensis* in the patient's buffy-coat cells by polymerase chain reaction. Serologic testing for leptospirosis, Lyme disease, and systemic lupus erythematosus was also negative. Serologic testing performed by the California State Department of Health Laboratories using the same *E chaffeensis* antigen showed an acute-phase titer of 1:40 and a convalescent (13 days later) titer of 1:640.*

Discussion

Ehrlichia species are obligate, intracellular gram-negative coccobacilli that can be visualized in infected patients' leukocytes and are members of the family of organisms that includes the genus *Rickettsia*.[4] The first proven human infection with an *Ehrlichia* species was described in Japan in 1953 and was caused by *Ehrlichia sennetsu*.[5] The illness described

*Neile R. Greene of the Centers for Disease Control and Dana Gallo of the California State Department of Health Services did the serologic testing.

was similar to infectious mononucleosis. Sennetsu ehrlichiosis thus far has only been reported from southern Japan and Malaysia.[3,6] The first case of human ehrlichiosis in the United States was reported in 1987; this illness resembled Rocky Mountain spotted fever but was without an exanthem.[1] The disease was attributed to *Ehrlichia canis*, the canine *Ehrlichia* agent. This and subsequent reports have shown that in the US human cases, serologic rises occur to *E canis* and not to *E sennetsu*.[4,6] Since the original US report, there has been increasing speculation that the US human agent is indeed not *E canis* but a distinctly new species.[2-4,6] The first organism of *Ehrlichia* isolated from a person in the United States has been recently identified by a team at the CDC and has been named *Ehrlichia chaffeensis;* it is genetically distinct from *E canis* and *E sennetsu*.[7,8]

Human ehrlichiosis, as described in the United States, is a multisystemic illness with many similarities to Rocky Mountain spotted fever. Prostration, severe headache, fever, malaise, myalgias, nausea, and vomiting occur in more than half of the cases; interstitial pneumonia, abdominal pain, jaundice, diarrhea, arthralgias, encephalopathy, and lymphadenopathy also may occur.[2] Rash has been described in 10% to 50% of patients, but in contrast to Rocky Mountain spotted fever, the rash is usually not petechial and can be subtle and transient.[2,3,9] Cerebrospinal fluid pleocytosis and meningeal signs may occur in ehrlichiosis, as they do in Rocky Mountain spotted fever.[2,10] Laboratory manifestations may also include hyponatremia, leukopenia (especially lymphopenia), anemia, thrombocytopenia, elevated aminotransferase levels, hyperbilirubinemia, azotemia, and evidence of disseminated intravascular coagulation.[2,3] Deaths do occur but probably less commonly than with Rocky Mountain spotted fever.[2,3] Although there is strong circumstantial evidence that the disease is transmitted to humans by ticks, the specific tick vector has not been proved, nor has a nonhuman vertebrate host been identified.[2-4] The human disease occurs mainly in the area of distribution of the Lone Star tick, *Amblyomma americanum*, and human illness occurs April through October (with the peak occurrence being May through July), times that correlate with the activity of this tick.[2,3] The treatment choice is one of the tetracyclines, although chloramphenicol is also effective. Penicillins, cephalosporins, aminoglycosides, and erythromycin are not effective; the efficacy of sulfonamides and quinalones, if any, is yet to be determined.[1-4,11]

This case illustrates the importance of obtaining an accurate travel history in all patients with unexplained, unusual illnesses, even when the travel is within the United States, and the need to know about illnesses that may be acquired in specific areas.

ACKNOWLEDGMENTS. Donald Conlon, MD, referred this patient to us. Robert Brennan, MD, of Lynchburg, Virginia, suggested the correct diagnosis; William Horbaly, MT, provided technical assistance.

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Blood-Saturated Operating-Room Shoe Covers

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THE IMPLEMENTATION of "universal precautions" in hospitals to prevent the spread of infectious disease has recently received much attention.[1(pp129-130)] Yet, blood contamination of surgeons' footwear through blood-permeable, paper operating-room shoe covers remains an unresolved issue. A special risk of shoe and stocking contamination with blood and amniotic fluid may exist for obstetricians during vaginal delivery and cesarean section. This study was carried out to assess the possible risk for shoe contamination with blood in operating rooms if standard blood-permeable shoe covers are used.

Materials and Methods

Disposable paper shoe covers were collected from the waste containers in the men's and women's operating-room dressing areas at the Tulane University Hospital, New Orleans, Louisiana. Each shoe cover was put into a biohazard bag. Shoe covers were collected within a two-day period at the end of each workday before trash collection and were then checked for blood. Because of the anonymous nature of this review, surgeons were not classified by surgical specialty or type of surgical case. The Tulane University Hospital is a general teaching hospital with essentially all standard surgical specialties represented. The covers were classified visually into three categories: covers with no blood, covers that blood had not soaked through, and covers that blood had soaked through. Shoe covers discarded in the nurses' lounge or the operating room were not examined. This may have introduced an underreporting of grossly contaminated shoe covers because the tendency may have been to dispose of such covers in the operating room.

A strip measuring 2 cm by 3 cm was cut out of one blood-soaked area on each shoe cover. This strip was then soaked for 30 minutes in a 0.9% saline solution to extract the pre-

(Summers PR, Biswas MK, Portera SG, Moore L: Blood-saturated operating-room shoe covers. West J Med 1992 Aug; 157:184-185)

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sumed blood spot. Negative and positive control specimens were included. Final confirmations of blood were accomplished with a phenolphthalein test (Kastle-Meyer test).[2(p610)] Initially 2 ml of extract was placed in a plastic conical centrifuge tube. Next, 2 ml of phenolphthalein reagent and 2 ml of 5% hydrogen peroxide solution were added to the tube. A color change to pink supported the presumption that the extract was indeed blood.

During five busy daytime periods, all surgeons were observed while taking off their shoe covers. The intent was to determine whether a sterile technique—that is, an effort to avoid blood exposure—was generally used. Observation was carried out without the knowledge of the operating room staff.

Results

Over a two-day period, 102 surgical shoe covers were collected from the dressing area for the operating room at Tulane University Hospital. Of those, 43 shoe covers showed no visible evidence of blood. Blood that appeared not to have soaked through to the inside of the shoe cover was detected on the outside of 27 shoe covers. A total of 32 shoe covers had visual evidence of blood soaked through to the inside. All cases of visibly identified blood were confirmed with a positive Kastle-Meyer test.

Many of the staff who were observed in the locker rooms did not wear gloves when removing the shoe coverings. Yet gloves worn by the investigators inspecting the shoe covers uniformly became contaminated with blood from the shoe covers, suggesting a risk of blood contamination to the surgeon with the removal of the shoe cover. Also, it was noted that some staff members walked in bare feet in the dressing area where shoe covers were removed, which may also present a risk of infectious exposure to the surgical staff. Of the 103 physicians observed, 84 wore contaminated shoe covers into the lounge-dressing area. Of the 84 physicians, 35 removed shoe covers with their bare hands and 35 removed shoe covers in the dressing area rather than immediately on entering. Only 7 washed their hands in the dressing area after removing the covers.

Discussion

The importance of infection control in the surgical area is obvious. Practical rules regarding surgical attire and mucous membrane protection have been well publicized, but the risk of blood contamination by operating-room shoe covers appears to be an unresolved matter of concern, at least at the Tulane University Hospital. This finding is probably typical for most general hospitals. Shoe covers not only carry possibly contaminated blood from the operating room to the dressing room area but also allow blood to soak through and saturate the surgeons' footwear. Further risk of blood exposure is evident when removing the contaminated shoe cover. Admittedly there was some potential in this study that shoe covers could have become contaminated after disposal. The potential for this was limited by the finding that shoe covers were generally inside out and crumpled up by the process of removal, protecting many of the contamination sites from contact with other shoe covers. Also, in some cases blood could have soaked through the shoe covers after disposal. The fact that blood could soak through the material was considered the more significant issue.

It is our opinion that the ideal shoe cover would minimize the risk of blood contamination for the surgical staff. Traditionally shoe covers were designed to prevent a transfer of contaminated material from surgeons' shoes to the operating environment. At one time, surgical shoe covers were also important to provide a ground contact when explosive anesthetic agents were in use. The role of shoe covers in the operating room should be modified to afford surgeons protection against blood exposure. The ideal characteristics of such a shoe cover would include the following:

- The shoe cover should be nonpermeable to blood,
- The shoe cover should have a nonwettable surface so that blood will tend not to adhere,
- The shoe cover should have some mechanism for easy removal that would minimize the risk of blood exposure at this point.

Shoe covers contaminated with blood probably should be removed with a gloved hand, and measures should be implemented to allow for the removal of shoe covers before entering dressing areas.

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Commentary

The 'R' Word

'Rationing' of Health Care and the Role of Academic Health Centers

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These days, analysts are evaluating everything about American health care; the most au courant technique is called "outcomes" research, which aims at assessing how much good or ill resul's from the interventions under study. If an outcomes study could be made of the use of the word "rationing" with relation to health care, I think researchers would conclude the word's use has been a disaster and would recommend banning it from our health policy working vocabulary. That the use of the word "rationing" radiates more heat than light, more confusion and ambiguity than clarity and precision, and more fuzzy thinking than logical analysis was illustrated dramatically at a recent international conference on the rationing of technology in health care held in Los Angeles under the sponsorship of the International Society of Technology Assessment.

The conference itself was excellent and provocative; it attracted a series of first-rate speakers, policy experts, health care professionals, payers, and consumers. But there was no agreement on what rationing meant. One interpretation was that it refers to the rational and fair allocation of goods; another extended the definition of rationing by specifying that the goods to be allocated were in scarce supply. Tore Scherstén, a noted Swedish surgeon, presented a third view, defining rationing as the limiting of access by patients to valuable and efficacious interventions that are thought to be beneficial to them. Currently this sort of rationing is carried out bureaucratically in many countries, and in the United States, by the marketplace and patients' ability to pay. There was much discussion pro and con among the experts about the merits of the Oregon approach to a public, prospective setting of priorities for health care interventions, so as to guide funding decisions among competing interests in the event that allocated funds for health care were limited. David Banta, MD, a distinguished American pioneer in the field of technology assessment who has spent much of the past decade working in the Netherlands, worried aloud that efforts at health care cost control in the European community may be beginning to have the chilling effect of discouraging beneficial innovation across the board.

Payers at the conference pointed out once again the role of physicians in the overuse of technology, but major emphasis was also given to the role of the public in demanding health care of questionable usefulness. The participants understood the importance of cultural determinants to controlling costs in health care; Per Buch Andreasen, a highly respected Danish physician, rose to comment that it was mind-boggling for Europeans to observe firsthand the extraordinary American fixation on healthy life-styles, healthy and beautiful bodies, and freedom from disease. Can we Americans learn to let go of life graciously, to die in season, and to resist the temptation to insist that every stone be turned to deliver to ourselves and our loved ones every last possible hour of life on this earth regardless of the enormous burden of increased, self-imposed suffering? Finally there was the difficult theme of physician control of the rationing process, with dissenting arguments coming from those physicians who feel deeply that the perception of their commitment to patients would be irretrievably damaged if patients were to think that physicians had the power to decide that, for whatever reason, a patient might not be worth saving with expensive intervention.

There was considerable discussion about the availability of care—the number of primary care physicians versus specialists, the presence or absence of gatekeepers—and what effect this has on the use of technology. The idea flickered across the stage that altering the proportion of primary care to specialist physicians might be the most effective approach to achieving a desired level of use of technology.

Only two things seemed to be widely agreed on by experts from the United States, United Kingdom, Denmark, Sweden, and the Netherlands:

- The escalating cost of health care across the western world mandates that choices be made and that unnecessary and inefficient interventions be scrapped;
- To make such choices rationally, more research and evaluation needs to be done on a continuing basis.

Even when and if the United States finds a financial plan through which to provide universal access to health care, the more serious task of figuring out what works and what does not will remain.

In 1984 Thurow and Fuchs, two of the nation's leading economists, wrote companion articles that clearly articulated these points.[1,2] They both concluded that it would be best if physicians did not have to make choices to limit treatments that were proved effective, but both agreed that physicians must insist on having available better data about what works and what does not.

The recent release of the National Leadership Coalition's Report on Health Care Reform[3] got widespread media attention but only on its admittedly extensive fiscal proposal and cost-control initiatives. No one seemed to take note of the major premise of the report that any approach to the so-called health care crisis needed to be systematic and not piecemeal. The media neglected to notice that, in addition to the financial dimensions of the report, there were other recommendations, including a section on quality, that if implemented

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would have perhaps the most far-reaching effect on our health care system. The National Leadership Coalition calls for a public-private commission that would determine, on the basis of the best available scientific evidence, which techniques work and therefore which ones will be paid for by either government or private health care dollars. This commission would also set priorities for research on unstudied interventions and techniques, allocating funds accordingly.

These recommendations are easier said than done. Yet the message is clear. If we want to make health care accessible to all, get the most for our money, and avoid a situation where we deny effective technologies to patients who need them, then we must develop the research required to evaluate the astounding health care technologies that will continue to spill from our research enterprises. If we can do a better job of ensuring the effectiveness and quality of that which is provided in our health system, there will be less of a need to use the "R" word and to argue about its definition.

If it is correct to establish an expanded and improved clinical evaluative research program as the linchpin of a more efficient and effective health care delivery system, then we have clearly laid a challenge at the doorstep of our nation's academic health science centers. There are several reasons why the academic community has not heretofore launched a more substantial health services research effort, including the following:

- There is not much money to support such research;
- No one gets tenure for doing multidisciplinary research, which many consider imprecise and inelegant and which frequently concludes that something does not work at all or well enough to warrant its use;
- The driving forces of our health industry have encouraged new technology without notable regard to cost.

Now, however, each of these forces has been countered, and there exist adequate incentives both outside of and within universities to facilitate their gearing up to do such research. There is a growing perception that a nation without better data on which to base decisions about the need for new techniques and technologies will be a nation more likely to reduce its support for the scientific base that spins off the growing array of new interventions. If society cannot turn to its universities for this function, to what other institutions can it turn?

Universities can help solve resource allocation problems in at least two other ways. Society can be encouraged to accept and demand reasonable limits to health services. The university is the place where public attitudes are being researched regularly, and society would be receptive to university-initiated discussions of the issues surrounding medical care in the last year of life. Universities, through their academic health centers, can regularly convene conferences aimed at educating professions and laity alike about the issues and options surrounding the health care reform debate. If it is true that our national debate has just begun, then we must strive to achieve as high a degree of public understanding of health-related matters as possible. Such an effort should most naturally be led by universities and their academic health centers.

Entering the next phase of the national health care policy debate perseverating over the word "rationing," with all its meanings, symbolic and real, will be unproductive and confusing to the public. On the other hand, arguing about how best to ensure and improve the effectiveness and quality of our techniques and technologies and, on a parallel track, discussing the best methods of determining how much we are willing to pay as a society for health care will constructively orient the debate so that citizens of good will can move together towards selecting societal programs that best meet our needs. This is what the National Leadership Coalition's much-heralded report has contributed, if we are willing to listen to its message.

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Commentary

Physician Aid in Dying
What Physicians Say, What Patients Say

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EDITOR'S NOTE: *This provocative paper by an activist member of the Hemlock Society—and the editorial comments that follow it—will, we hope, stimulate your thoughts and illuminate murky areas as pressures mount about how physicians can best serve patients.*

In talking to physicians and their patients, I have found that the two groups do not communicate well about patients' choices at the end of life.

Many persons strongly believe that someone with a terminal or hopeless illness should have the right to ask a physician for aid in dying. Many physicians disagree. I offer the following imaginary dialogue.

PHYSICIANS: *My patients never talk to me about wanting to die.*

PATIENTS: I would never mention it to my doctor. I would be too intimidated. I would worry that he or she would be angry. The subject is too private and too frightening to discuss with him or her. Anyway, in the little time we have to talk, my physical well-being is the exclusive subject. My doctor knows very little about the rest of my life, let alone my most personal values and feelings.

Of course, I would follow a patient's instructions regarding the durable power of attorney or living will; that should be enough.

We hear distressing stories about doctors who do not follow those directives—and it is the law. Even when they do, it's not always enough. What if I or my surrogate refuses medical treatment, such as chemotherapy, dialysis, antibiotics, or surgery—then what? It is possible that I will have a lingering, painful, degrading, and expensive death. I may want to end it before then, with your help. Will you just walk away after you've pulled the plug? What if I have no treatment to refuse or withdraw? How do I die if the quality of my life has deteriorated beyond any point acceptable to me? The law does not go far enough.

Pain is a problem that can be controlled.

Pain is not the main reason that most people ask to die. Degradation and loss of dignity at the end of life because of incontinence, the inability to swallow or to speak, the need to have 24-hour-a-day care, not being mobile, or not enjoying any quality of life are conditions that motivate patients to want help in dying. Also, many patients do not want the heavy sedation and side effects that accompany high levels of pain medication. And, finally, there remains a small percentage of patients whose pain is not controllable by medication; they should have options.

Hospice care is all people need.

Hospices are very important and a great source of comfort to those of us who can avail ourselves of their services and be reassured of a peaceful death with compassionate care givers. For some, a hospice is not available where they live, they do not have a caretaker to work with a hospice, or they choose not to use the service. Even for those who do use a hospice, a lingering death should not be the only option. Hospice care, albeit skilled and thorough, cannot always mitigate the agonies and indignities of dying. Ideally, a person could choose a hospice service that would also provide aid in dying on the written, repeated, witnessed request of a competent adult patient.

Patients do not want physician-assisted suicide; this comes primarily from the Hemlock Society, which is a small, fringe group.

Survey data published in a recent issue of the *Journal of the American Medical Association* showed that 64% of Americans thought that when a terminally ill patient is conscious and in pain, physicians should be allowed by law to respond to a patient's request for lethal drugs or injections to aid in dying. Support was strongest from younger people (79% between the ages of 18 and 34), and of all religious groups, Catholics favored it the most (72%).[1] Almost half of the voters in Washington State endorsed Proposition 119 when it was on the ballot last year.

Physicians do not want this option.

The consciousness of physicians about patient self-determination has changed over the past few years—with the help of the courts—including the right of a patient to refuse medical treatment, as guaranteed now by the United States Constitution in the 1990 Cruzan decision.[2] Some physicians now agree that letting a patient die by withdrawing treatment is not sufficient; a patient should have the right to ask physicians for help in dying. In a 1989 article by 12 physicians and ethicists on physicians' responsibility to hopelessly ill patients, 10 of the authors endorsed the idea that a physician should help end the life of a hopelessly ill patient if that is what the patient wants.[3] A more recent article described a physician's experience in assisting the suicide of a patient.[4]

Do you doubt what options doctors would want for them-

(Girsh FJ: Physician aid in dying—What physicians say, what patients say. West J Med 1992 Aug; 157:188-189)

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selves if their quality of life were hopelessly diminished by a terminal illness? Most would want to have the choice to end their lives, even if they never exercised it.

This approach is a violation of the Hippocratic oath.

The Hippocratic oath is being administered less often to graduating physicians, probably because it reflects an era of paternalistic medical practice. The alleviation of suffering is as much a part of traditional medical care as is the prolongation of life. More important, patients are realistic enough not to expect perpetual cures from their doctors; death happens. When it approaches, we want the same careful, caring concern and help that we expect when we ask doctors to treat us or at least to help us with our suffering.

Patients trust physicians. We will not let you down.

We do trust you; that is why we want you to help us at the end of our lives. But we do not want to jeopardize doctors' practice of medicine by asking them to perform an illegal act. And we should be the ones to determine when pain is too much, suffering unbearable, and our quality of life unacceptable. We want our choices documented and agreed to, so we do not have to rely on a good-faith contract when we are desperate for help. We want our agreement with you documented so both of us will be protected. In the increasingly impersonal world of medical care, your reassurance that you will not let us down is not enough. If you do not want to help in the way that we would like, we want you to refer us to someone who will.

Suicide is never acceptable.

We agree that suicide is not a way to solve emotional or mental problems, but the wish to end life when the quality and dignity of our existence have been irreversibly eroded and death is inevitable is not irrational. Thoughtful people make this choice. After one has lived a useful, productive, and influential life, is it irrational to wish to exit peacefully and with dignity amidst loved ones? For those for whom suffering is ennobling and hope is eternal, this option does not need to be exercised.

Assistance in dying should be handled by the family.

If you have ever had the experience of a husband helping a beloved wife to die, a daughter helping her mother, or, the worst case, a parent helping a child, you know the agony involved. It is hard enough for a family member to make the decision to withdraw or refuse treatment; that person should not have to do the physical act of assisting in dying unless it is by choice and it is legal. A patient should not have to die without a loved one present, but patients should not put relatives or partners in legal jeopardy by asking them to help or even to be there under the present system.

Physicians have legal access to medications that can help someone die quickly, gently, painlessly, and surely. They know the patient's tolerance to morphine and what the pharmacologic alternatives are.

This approach is against my religious or moral beliefs.

Make sure you tell me that when I ask. Is it also a problem to care for me if I or my surrogate refuses medical treatment that you recommend, even if it would save or extend my life? I want to know that, too. Many doctors hold beliefs that are counter to patients' self-determination and even to informed consent. I want to be told all the alternatives, and I want to know what you believe that may bear on how we communicate about my treatment or lack of it. My beliefs do permit me to end my suffering; I want my physician to respect my beliefs and to inform me in advance if he or she could not in good conscience do so.

The request for help in dying may stem from depression.

It is true that people with hopeless, painful, degrading diseases may become depressed. The physician can suggest treatment for depression that the patient may or may not accept.

Once this begins, what's next? It's a slippery slope.

We are on a dangerous, slippery slope now. By pretending that aid in dying never happens, we allow the possibility of involuntary euthanasia to occur where someone else—not the patient—is making the decision.

The current law is being ignored. Police are not reporting mercy killings and assisted suicides; district attorneys are not prosecuting them; grand juries are not indicting; and, when a rare case does go to trial, juries are acquitting. Is this better than having a law that would provide regulations about a practice that desperate people are exercising surreptitiously?

Those who cannot afford medical care or who are seen as a drain on the system will be pressured into being eliminated.

Is it good public policy to penalize those persons who want choices at the end of life to protect paternalistically a class of people who also may want the choice? There are other ways to safeguard the rights of the poor and socially stigmatized than by depriving everyone of the right to choose how they will die. The system of inadequate and nonexistent health care for the uninsured and underinsured now passes tacit death sentences on the poor through neglect. We should make our medical system more equitable and humane so that no one will choose to die because they can't pay for medical care or because nobody cares what happens to them.

Physicians cannot be healers and killers.

Helping a terminally ill patient die at his or her request is at one end of the continuum of lifelong medical care when healing becomes impossible, as it does in every life. For a physician to walk away from a patient at that juncture and say, "Now I no longer have the tools or skills or will to help you" is truly inhumane. It makes the final passage of life a lonely, fearful one rather than one that brings peace and true termination to a full life. It is healing to reassure patients that you will be there for them if that is their choice.

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Editorial Comments

Assisted Suicide—What Euthanasia Activists Say, What People With Disabilities Say

As our society considers legalizing euthanasia, we hear much talk about a "slippery slope." Supporters of euthanasia claim we can limit it to terminally ill persons who choose that option for themselves. With strict guidelines, we can protect socially stigmatized and therefore vulnerable persons from being pushed into their graves. The trouble is that these same activists have long advocated "voluntary" euthanasia for people with disabilities.

A much-publicized example occurred a decade ago when euthanasia activists championed a request for the physician-assisted suicide of Elizabeth Bouvia, a 26-year-old California woman with quadriplegia due to cerebral palsy. At age 10 she was put in the first of a succession of institutions. At age 18 she began to live independently, hiring aides to do her housekeeping services and assist her with bathing, dressing, and eating, paying them through California's In-Home Supportive Services program. Although legally entitled to maximum financial aid, Bouvia received considerably less, in violation of state guidelines.

Bouvia also sought an education, earning a bachelor's degree at San Diego State University and then enrolling in the master's program in social work there. The school did not support her when a local hospital violated her civil rights by refusing to make "reasonable accommodations" that would have enabled her to get field-work experience. One of her professors also told her she was unemployable and said the school would never have admitted her had they known just how handicapped she was. Despairing of achieving her professional goal, she dropped out of school. Meanwhile, she married but kept her marriage secret from welfare agencies for fear of having her vital financial aid reduced or eliminated. Bouvia then suffered a series of additional tragedies: Her brother drowned. She became pregnant and had a miscarriage. She separated from her husband and sought a divorce. It was at this point that Elizabeth Bouvia checked herself into Riverside County Hospital's psychiatric unit and asked for help to end her life.

When the hospital refused, Bouvia engaged a team of volunteer lawyers to file suit. They brought in a physician, a psychiatrist, and an educational psychologist to assess her mental state. Although she told these evaluators of the emotionally devastating experiences she had suffered, they concluded that because of her disability she would never be able to achieve her life goals, that the disability was the reason she wanted to die, and that her decision for death was rational. Both Richard Scott, the head of the team of lawyers, and Faye Girsh, EdD, the educational psychologist, were active members of the Hemlock Society.[1]

Failure to understand the experiences that drive a disabled person to suicide is not confined to euthanasia advocates. It has been the basis of court decisions granting assisted suicide to disabled persons while calling it "refusal of medical treatment."[1] In 1985 Larry McAfee, a civil engineer residing in the state of Georgia, sustained a high-level spinal cord injury in a motorcycle accident. With quadriplegia and continuously breathing on a ventilator, he nonetheless concluded in rehabilitation that he could return to work as a computer consultant. In May 1986 he began to live independently, helped by personal-assistance personnel, but by November 1987 his insurance settlement money had run out. Georgia funded only nursing home care, not independent living, and no Georgia nursing home would take McAfee, so he was shipped off to a facility in Ohio. In January 1989 Ohio Medicaid refused any longer to pay for the care of a Georgia resident and ordered his return to Atlanta, where he was placed against his will in Grady Memorial Hospital's intensive care unit. After three months in that highly stressful environment, he enlisted a lawyer to file a legal petition for physician-assisted suicide. In August 1989, after eight months in the intensive care unit, he was transferred to a nursing home in Alabama. In September an Atlanta judge read amicus briefs filed by the Georgia Medical Association and the Catholic Archdiocese and heard testimony from a medical ethicist and a Baptist minister, all supporting McAfee's request. Approving the petition, the judge ruled that his death would not be suicide but merely a refusal of medical treatment. In November the Georgia Supreme Court upheld the decision.[2]

Over the next few months, Larry McAfee's interest in independent living and a career in computer consulting revived. The obstacle was not his severe disability but whether independent living rather than nursing home confinement would be funded. In January 1990 McAfee testified before the Georgia legislature in behalf of state funding for independent living. He cited his own experience to warn what can happen to a disabled person in the absence of such assistance.

Larry McAfee described the social death that is commonly inflicted by society on people with major disabilities. Because they are regarded as socially dead already, assisting their physical deaths can be justified easily. Advocates of aid in dying reinforce those notions by equating disability with terminal illness. The Atlanta court ruled that McAfee's act would not be a suicide because the ventilator was merely "prolonging his death" (D. Riner, "A Matter of Life and Death, Judge Rules Man Can Disconnect Ventilator," *Atlanta Constitution*, September 7, 1989, p A17). Scott and his colleagues had similarly argued for Bouvia's right to assisted suicide by likening her condition to that of a terminal patient.

Euthanasia advocates frequently equate disability with terminal illness. The "living will" disseminated by the Society for the Right to Die says,

> I direct that life-sustaining procedures should be withheld or withdrawn if I have an illness, disease or injury, or experience extreme mental deterioration, such that there is no reasonable expectation of recovering or regaining a meaningful quality of life.[3]

The word "terminal" does not even appear here. Virtually any major chronic condition might be an appropriate occasion for physician-aided death. The living will ignores the social realities that can deny people with disabilities a "meaningful quality of life." Three of the four women whose suicides Jack Kevorkian, MD, assisted had disabilities, not terminal illnesses. At the beginning of her "imaginary dialogue" elsewhere in this issue,[4] Dr Girsh implicitly lumps handicapped people with those who are terminally ill. Who "should have the right to ask a physician for aid in dying"? Her answer: "a person with a terminal or hopeless illness."

The most authoritative pronouncement on this subject

came from the Hastings Center (Briarcliff Manor, New York) in its 1987 *Guidelines on the Termination of Life-Sustaining Treatment and the Care of the Dying*. These guidelines cover not only persons who are terminally ill but people with a "disabling condition that is severe and irreversible."[5(p28)] They also make cost-worthiness a consideration in deciding whether to continue medical treatment.

The "slippery slope" image implies that the extension of assisted suicide to socially stigmatized persons would occur inadvertently, unconsciously, and unintentionally. That image conjures up the specter of a progression from euthanasia for only terminally ill persons to the coerced deaths of those who are devalued but not dying. But neither aspect of the metaphor accurately represents what has been happening. Although no state has yet adopted a euthanasia statute for terminally ill persons, advocates of such laws have pressed for court rulings to guarantee persons with major disabilities the "right" to physician-assisted suicide. In the Bouvia, McAfee, and Rivlin[6] cases, courts in California, Georgia, and Michigan granted such requests. This is not an unintended slide down a slope. Suicides of disabled persons are already being socially and legally sanctioned.

The health care system and the courts must stop abetting the suicides of disabled persons. Three guidelines should be adopted:

- We must repudiate the notion that assistive devices and services for severely disabled persons are merely prolonging their dying. We must reject the argument that bids for assisted suicide by disabled persons are refusals of medical treatment. Equating disability with terminal illness reflects not a person's medical condition but their devalued social status.
- Persons with disabilities who request assisted suicide must be evaluated by professionals knowledgeable about the psychology of disability and the oppressive social experience of people with disabilities in this society. The misunderstanding of Larry McAfee, David Rivlin, and Elizabeth Bouvia by their psychiatric examiners demonstrates that evaluation by professionals with appropriate expertise is absolutely essential.
- Any body convened to discuss the euthanasia issue or to draft or apply rules governing the refusal of medical treatment must include representatives of the disability-rights community. Symposia to debate aid in dying commonly do not include discussants from that perspective. (This journal is a notable exception.) In the Bouvia and McAfee cases, the courts welcomed and even solicited the views of nonhandicapped persons but ignored the amicus briefs filed by disability-rights groups. No disability-rights leaders were included in the drafting of the Hastings Center guidelines. The disability-rights community has a distinctive perspective to contribute to this public debate. Given that the lives of people with disabilities are at stake, including that viewpoint is a matter of social justice.

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The Popular Movement for Physician-Assisted Dying—What the Public Is Saying, What Physicians Are Hearing

SHORTLY AFTER Jack Kevorkian, MD, helped Janet Adkins kill herself in June 1990, a colleague and I wrote an article urging the profession of medicine to take seriously the increasing public voice asking for aid in dying.[1] It seemed to us that in the media furor following the first Kevorkian case, the "voice of the profession" was heard as a unitary one—rejecting thoroughly and unconditionally the idea of physicians helping people die as being immoral and inconsistent with medical ethics. We thought that the Kevorkian case was so bizarre as to obscure the more real-life cases that go on every day. We were also impressed by the consistency of the data showing that a majority of people in the United States favor policies that would allow them aid in dying when they are terminally ill, and they would prefer physicians to help rather than family members. In the face of this consistent public opinion, the rigid Hippocratic stance seems an inadequate response; we should at least be asking ourselves what this public debate means to our patients.

In the past two years, there has been much more open discussion within the medical profession, especially in the wake of an article by Timothy E. Quill, MD, in the *New England Journal of Medicine* describing his personal experience in physician-assisted suicide.[2] I hope that discussion will continue. Informal discussions among physicians make it clear that this practice is not a new one; it has probably been going on covertly in the intimacy of the doctor-patient relationship throughout the history of medicine. In a recent survey by the American Society of Internal Medicine, 20% of respondents said they had assisted a patient's dying in response to requests by the patient.[3] In her commentary in this issue, Faye Girsh, EdD, says that younger physicians are increasingly accepting physician aid in dying as a patient's right,[4] but in discussions with my colleagues, it seems that older physicians are much more likely to be flexible on this topic, particularly if they have cared for patients in the throes of terminal illness. It is the experience of many years that brings physicians in practice face to face with these important dilemmas. Younger physicians may be more likely to see the issue in black or white terms rather than in its thoroughgoing and extensive grayness.

In the past, these acts of mercy on the part of physicians were probably better kept cloaked within the privacy of the doctor-patient relationship. Modern medicine has lost the ability to conduct its work in that kind of silence, however. We are now called on to be accountable to the public for both standards of ethical practice and standards of competent medicine. In this context, in most states participation in physician-assisted dying is still illegal. It is unrealistic to ask physicians even in extreme and unusual circumstances to take the risk that breaking the law would entail. Interestingly, recent reviews of the law in this area suggest that in most cases—unlike the Kevorkian situation—where there is a longstanding doctor-patient relationship and where the physician is clearly acting with merciful motives, charges are always

dropped or sentences suspended. It is as if the law must assert its condemnation of killing and yet make an internal exception at the level of the judge and jury when these kinds of special cases arise. But in this new, open environment, it could be argued that policies should reflect what is actually happening rather than an idealistic but unrealistic standard. Real threats of abuse exist, and yet there is no reason to think that legalization will bring more abuse than allowing the practice to go on covertly.

The profession also should ask itself whether public insistence on aid in dying indicates other failings in the care of dying patients. Here we have a lot to learn, and should we be able to make progress, we could probably prevent a good deal of emotional anguish around terminal illness for both patients and their families. With the single exception of hospice care, the skills of which are not routinely taught in residency training or practiced in most acute care hospitals, the medical profession is woefully ignorant of and unable to conduct compassionate comfort care. Patients are therefore left to believe that their only choices are acquiescence to unrestrained life-sustaining technology or abandonment by their physician. With this kind of a choice, it is not surprising that people facing terminal illness might want some control over the time and manner of their demise.

Dr Girsh has made an important addition to this vigorous debate by her hypothetical dialogue between physicians and patients on this topic.[4] She raises many of the most common objections we hear from physicians on this topic and presents thoughtful responses that I hope will stimulate discussion among physicians' groups on medical staffs of hospitals, in practice, and in specialty societies.

This editorial was written while Dr Cassel was a fellow at the Center for Advanced Study in the Behavioral Sciences, Stanford, California, where her work was supported by a grant from the Henry J. Kaiser Family Foundation.

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Death, Politics, and Philosophy

CONSTANT MEDITATION on death is good for the soul, said our religious forebears. The citizens of Washington State meditated on death recently but not constantly. They meditated only long enough to decide how they would vote on Initiative 119, which would have authorized physicians "to effect the death of a patient in a dignified and swift manner." November 5, 1991, brought voters to the polls to vote on three eternal verities: death, as in euthanasia and abortion; taxes; and the perfidy of politicians. After brief meditation, they affirmed by a close vote a woman's right to abortion and negated a patient's right to choose aid in dying. In so doing, they decided that Washington State would not become the first jurisdiction in the world to make active euthanasia legal.

The prepoll meditation on death convinced more voters to mark no rather than yes, even though earlier surveys had indicated the opposite. Why they did so is uncertain: Proponents claim mendacious television advertising—of which they were not themselves innocent—misled voters to believe there were no safeguards against abuse. Perhaps the gruesome exploits of Jack Kevorkian, MD, who aided two women to die several days before the election, turned the voters' hearts away from merciful death. More likely, many voters realized that "death with dignity," the title of the initiative, was not the issue but that an unprecedented legal authorization of the healing profession to take life was. They were unready to grant that authority.

This was wise, for they were persuaded that the proposed amendments to state law did not have adequate safeguards against abuse. Although literally limited to voluntary patients who were terminally ill and who competently requested their physicians to end their life, the law seemed to insulate this decision so tightly from oversight and scrutiny that the slippery slope lurked ahead. Who would know whether a less-than-competent patient had been aided to die because they "would certainly have asked for help, had they been able"?

The proponents of Initiative 119 denied the opponents' allegation that the law afforded only weak protection against abuse. At the same time, their colleagues in the Hemlock Society offered legislation in California that added several of the safeguards critics found lacking in the Washington proposal. When the issue comes to the voters again, whether in California, Washington, or elsewhere, it will be more difficult for the opponents to defeat. The safeguards whose absence they criticized will be included. Opponents will have to move to a more philosophical and less easily argued plane.

The arguments will circle around the questions and answers stated so eloquently by Faye Girsh, EdD, in this issue of the journal.[1] I say "circle" because around each of her statements stands a set of arguments that can become deeply philosophical and, if you will, theological. These sorts of arguments are difficult to pose and to follow, even for persons adept at philosophy and theology. They certainly are not reducible to the infamous sound bites that suck all the substance out of important ideas. Still, in the long run, each of us, considering and appreciating the arguments as best we can, must come to a personal judgment.

During the political campaign in Washington State, I was an opponent of Initiative 119. My opposition stemmed largely from the public policy and legal drafting problems that I saw in the initiative. As a professor of medical ethics, I also have what I think are deeper philosophical objections. Yet I must admit that as we debated, I found my philosophical objections becoming somewhat less persuasive and the propositions of those philosophers and ethicists who favor active voluntary euthanasia becoming more plausible. A month after the election, I attended a small conference of ethicists and physicians, sponsored by the Kennedy Institute of Georgetown University (Washington, DC) and the Johns Hopkins School of Medicine (Baltimore, Maryland), where I heard discussions on the highest philosophical plane that left me wondering even more about my previously firm opposition.

Then, a few weeks later, the political debate and the philosophical arguments turned personal. I sat by the side of a dying relative very dear to me. At age 90, he was simply wearing out. A proud, fastidious, and philosophical man, he had been reduced in several weeks to incoherence, incomprehension, and incontinence. Not in great pain, he was clearly uncomfortable and restless. A physician himself for more

than 50 years, he had stood by the bedside of many dying patients. He had been ahead of his time in appreciating his patients' "right to die" and had scrupulously refrained from prolonging their death. He had asked not to have any extraordinary measures taken to prolong his life, and his own physician respected that wish. He was at home, in his own bed, with his cherished wife at his side. Yet his last days were agony to us and apparently to him. When I whispered to him, "We are not holding you back," he murmured, "You are, you are. Why are you holding me?"

Inevitably, I had to reflect, would it not be better for all to end this now? An injection, a potion, could cut short this undesired misery. Although my uncle had always repudiated active euthanasia in our discussions about medical ethics, might he not now accept it in his present condition? Should not we who loved and respected him take that decision in his best interests? Indeed, if a law like Initiative 119 were in place, we could have asked him his wishes while he was still coherent, and he could have ordered his own death before decline. Any competent physician could have judged from his general medical condition that he probably had less than six months to live and thus could reasonably be designated as terminally ill.

I wondered why I should say no any longer to the humane proposal of active, voluntary euthanasia. I knew that in my role as professor of medical ethics, I would again have to address the issue publicly. If adequate safeguards were in the next version of any proposal, how could I oppose it?

I again meditated on death and, again, I found myself in the camp of the opposed. I suspect my late uncle would be there as well, even though he was the sufferer of terminal indignity. My meditation ushered in that conclusion because I believe that if we abolish terminal misery from our experience, we will foolishly hide an essential measure of our humanity.

Active euthanasia for the voluntary and competent patient seems so plausible and liberal. Yet it suggests a technologic solution to a perennial human problem. We can efficiently abolish not death but dying, the process that leads to death. We can hide the misery but not the ultimate fact itself. If we can ethically and legally do that for the requesting person, why not for each and every sufferer of terminal misery? The possibility of swift and painless death will inevitably become the necessity. The privilege granted to the competent will be seen as a right of which others less fortunate than the competent should not be deprived. In the end, banishing the misery of dying may not be the undiluted benefit that it appears to be from a distance.

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Physician Aid in Dying—Finding the Middle Ground

IN THE ANCIENT Christian litany, there is a section that reads, "From sudden death, good Lord, deliver us." How times have changed. With advances in medical technology and the pharmacopeia and a loss of the long-term understanding of patients and physicians who had known one another for years, we are at a point where a large and articulate body of the population are so afraid of their physicians' ability to keep them alive that they seek that same physician group to help them die and to free them from lingering, miserable despair.

What is death with dignity, anyhow? Those who speak of it, I think, mean a death with the retention of pride and self-respect to the absolute point of death, and because, in our society, self-control, continence, mobility, intellect, and independence are equated with self-respect, people who lose this control over self would often sooner die. But as Faye Girsh, EdD, asks in her article in this issue, what if they cannot bring about their own deaths?[1] Should physicians be morally or legally obliged to help them or to refer them to sources of help?

A right is something that belongs to a person by law, nature, or tradition. Because nature provides us with an obligation to die, it hardly seems necessary to proclaim it as a right. Neither is it traditional for our society to approve of euthanasia in humans. Thus do the Hemlock Society and those who agree with the Hemlock Society speak of the institution of a right under the state through an act of legislation. But this law giving people the right to die also involves the rights of physicians. Shall those who feel that aid in dying is morally opprobrious be compelled by law or custom to participate in it, even by referral? Is there any precedent for a law that requires one human being to help execute another, even at their own request and with their complete concurrence? There are societies in which tradition dictates this, as in the *seppuku* of Japan, in which a person may be asked in honor to decapitate a friend who is disembowelling himself in an act of hara-kiri. But the law does not compel such an act of friendship. Even the executioners of those legally condemned in the United States are volunteers.

Will physicians volunteer to do this? I think many may because there are physicians who firmly believe that it is part of their service to provide that final comfort and to acknowledge that a patient's despair or pain may be irremediable by any currently known therapeusis, all avenues having been exhausted. Then we must ask, if such physicians choose to perform euthanasia at the request of the patient, should there be a law that allows them to? Not even in Holland has such a law been enacted, though euthanasia is officially permitted by a failure to enforce the current law, which stands against euthanasia.

I have three concerns about these complex issues: The first is that the "right to die" seems to translate in practice to the right to a controlled and comfortable death, even at times a convenient death. By this I do not mean to trivialize the motives of those who are eager for release from the unendurable, but, in the harsh light of analysis, it is this emphasis on control, comfort, and convenience that appears to be paramount in the arguments of those in favor of an aid-in-dying statute. Unfortunately, what is convenient and comfortable may be largely defined by social mores and thus differ from time to time and place to place. Is the loss of mobility so great a loss that one would sooner die than endure it, as in quadriparetic patients? Is incontinence so embarrassing that one would sooner die than endure it? Is the inability to swallow or to speak or the need to have help 24 hours a day so degrading? Some of these losses are socially defined, and patients who suffer them may feel themselves to be a burden to such a degree that they would choose to die. Certainly this will grow

worse as larger and larger numbers of the elderly reach points at which full function is compromised. The economic pressures on the elderly to not sap the resources of their families will grow greater and greater. How shall we prevent the patient from, like the Hindu widow throwing herself on the funeral pyre of her dead husband, feeling socially compelled to die?

We should also openly discuss the major difference between the ethical probity of euthanasia, with which many concur, and its legality. Dr Girsh suggests that legalizing euthanasia will make it easier for persons seeking aid in dying. This is to my mind by no means certain. Abortion is currently legal, but this has not legitimized abortion in the minds of many who oppose it with vehemence. The argument that legalizing euthanasia will make it easier to obtain and that surreptitious euthanasia, such as now occurs, is less desirable may face some harsh reality when the first group of protesting pickets appears on the hospital steps or at the door of the home to participate in what heretofore had been a private interaction among the patient, the patient's family, and the physician. There may be some value in underground activity, at least as regards control, convenience, comfort, and dignity.

Perhaps at the core of the matter is informed consent. We have, both patients and physicians, grown accustomed in the past decades to the idea that any logical decision in medicine depends on weighing the alternatives and the risks and benefits of any procedure. The patients and the physicians engaged in aid in dying are presumed to be fully aware of the risks of continued life. What, however, are the benefits of dying? This is, at the very least, highly contentious. Though this may be argued by the religious of various creeds, I personally do not know what lies beyond death. For this reason, I cannot give my patients the risks and benefits of the state of being dead. One of the reasons I suspect physicians so desperately keep patients alive is that it gives them and the patients a continuing chance at yet another decision and thus—as opposed to what Dr Girsh says—actually preserves the patients' rights and autonomy because, so far as we know, the dead have no further choices. We do not do surgical procedures predicated on what patients believe the results will be but rather on what we in our best medical judgment anticipate the results will be. Should we render patients dead predicated on what *they* believe death is like or what *we* believe death is like? This may be a conundrum beyond answering.

Finally, the issue is not as polar as Dr Girsh implies: Help the patient to die or just walk away. Most physicians and patients work within a middle ground, where all help possible is given for as long as possible. Everyone would concur that to abandon a person who is in pain or despair is reprehensible. If a physician abandons a patient because the physician decides there is no more active therapeusis, that physician needs retraining in simple human skills. We need more emphasis on the alleviation of pain, systems for restoring dignity and worth to the impaired, and the comfort of those in despair before we "solve" the problem by helping them to die.

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Editorials

Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia

In 1836 Richard Bright commented on the progressive fading of the "healthy colors of the countenance" of his patients,[1] and ever since anemia has been considered a hallmark of his disease. The pathogenesis of this anemia is complex and involves a shortened red cell life span due to hemolysis and blood loss without an adequate compensatory increase in the rate of red cell production. This lack of compensation was thought to be due primarily to erythroid suppression by uremic toxins. In 1957, however, studies by Jacobson and coworkers suggested strongly that the newly described erythropoietic hormone, erythropoietin,[2] was produced by the kidneys and that a relative erythropoietin deficiency in patients with kidney failure would explain the lack of bone marrow compensation.[3] It was not until it was found that isolated perfused kidneys can synthesize erythropoietin[4] and that messenger RNA for erythropoietin is present in anemic kidney homogenates[5] that the Jacobson hypothesis was fully accepted.

The recent observation that treatment with recombinant erythropoietin can restore the hemoglobin concentration to normal has shown that erythropoietin deficiency must be the most important pathogenic mechanism for anemia.[6] Of course, this finding does not rule out the presence of other mechanisms since a large dose of erythropoietin could have stimulated the rate of red cell production sufficiently to conceal an increase in red cell destruction or a uremic bone marrow suppression. In well-dialyzed and carefully managed patients, however, red cell survival is usually normal and the existence of a uremic bone marrow toxin has been exceedingly difficult to establish.[7] Furthermore, there appears to be an almost identical effect of erythropoietin in normal and uremic sheep,[8] strongly suggesting that uremia per se does not suppress red cell production. Nevertheless, we still do not understand why the level of circulating erythropoietin in anemic and uremic patients is often increased to levels capable of maintaining a much higher hemoglobin concentration in anemic patients with normal kidney function.

The spectacular success of recombinant erythropoietin therapy in ameliorating anemia both in dialysis patients and, as described by Pinevich and Petersen in this issue of the journal, in predialysis patients[9] has made a search for the exact pathogenic mechanism of anemia a little less urgent. Erythropoietin therapy works, it has relatively few side effects when used sparingly, it improves quality of life, and, despite its price, it is cost-effective by eliminating transfusion requirements. Furthermore, as emphasized by Pinevich and Petersen, an increase in hematocrit with a corresponding decrease in renal plasma flow does not, as could have been expected, affect renal function or the progression of kidney failure.[9]

The effectiveness of erythropoietin as a replacement agent in the anemia of kidney failure raises the question if exogenous erythropoietin can be of use in the treatment of anemic patients with intact renal function. This seems logical if the anemia is associated with subnormal levels of plasma erythropoietin such as occurs in patients with anemia of chronic disease.

Chronic disease is a somewhat motley designation for a sustained but not life-threatening illness. Anemia is a common denominator, and a number of studies suggest that one cause is an inadequate production of erythropoietin in response to anemia. Such a blunted response has been noted in patients with rheumatoid arthritis,[10,11] carcinoma,[11,12] lymphoproliferative disorders,[13] sickle cell anemia,[14] and human immunodeficiency virus infection.[15] It is tempting to invoke the action of inflammatory cytokines such as interleukin 1 and tumor necrosis factor on the renal biosynthetic mechanism responsible for the production of erythropoietin. Studies of erythropoietin production in hepatoma cells and isolated rat kidneys suggest indeed that these cytokines can suppress erythropoietin synthesis in response to hypoxia.[16] Unfortunately, the kidney is still a black box as far as an understanding of the relationship between the anemia and erythropoietin synthesis goes, and we need more basic information about the biosynthesis of erythropoietin before we can explain the blunted response in chronic disease.

For whatever reason the renal synthesis of erythropoietin is blunted, recombinant human erythropoietin should be of value as a replacement agent. This has been shown to be the case in therapeutic trials of patients with rheumatoid arthritis[17] and several other chronic illnesses.[13,18-20]

Because the use of erythropoietin is still expensive and demands parenteral administration, it is necessary to judge if a mild to moderate anemia in patients with chronic illnesses is a problem worth treating. Undoubtedly the anemia in some is a burden that needs to be corrected, but in many it is merely an asymptomatic nuisance.

In anemia not associated with a subnormal production of erythropoietin, the administration of recombinant erythropoietin may also be of value by boosting red cell production and partly replacing the need for endogenous erythropoietin. In chronic hemolytic anemia, the rate of red cell production is increased to balance a shortened red cell life span. This balance is first achieved when the red cell mass is decreased. Such a decrease reduces the volume of blood hemolyzed and replaced every day and provides the hypoxic drive necessary for the production of erythropoietin and in turn for the production of red cells. The administration of exogenous erythropoietin should relieve the pressure to produce endogenous erythropoietin and result in setting a new balance at a higher hemoglobin concentration.

In patients with chronic bone marrow failure, the hemoglobin concentration is also reduced until anemic hypoxia generates enough erythropoietin to stimulate a sluggish marrow to offset the daily destruction of a fortunately reduced red cell mass. The administration of exogenous erythropoietin replaces some of the endogenous erythropoietin and decreases the need to maintain a low hemoglobin level.

A number of clinical trials are under way to test these suppositions, and the results are still being evaluated. Unfortunately, the most desirable forms of anemia to treat are those in which a balance between production and destruction cannot be achieved without the use of blood transfusions. Because the rate of red cell production of a normal bone marrow, regardless of the amount of erythropoietin available, cannot exceed six to ten times baseline production, it cannot compensate for severe hemolysis. Similarly, aplastic bone

marrow or bone marrow with severe or ineffective red cell production cannot be stimulated any further regardless of the amount of erythropoietin available. Consequently, the administration of exogenous erythropoietin in patients with chronic bone marrow failure will probably be of little value. This has been found to be the case in myelodysplastic syndromes in which only a few patients receive any benefits from exogenous erythropoietin administration.[21-25]

As is evident from these remarks, it is difficult to predict if the administration of recombinant erythropoietin will be of therapeutic value in patients with nonrenal anemia. In patients with moderate anemia and an erythropoietin concentration of less than 100 U per liter, it is reasonable to assume that erythropoietin production is subnormal and that, if clinically indicated, a therapeutic trial of recombinant erythropoietin is justified. In patients with more severe anemia and especially if the erythropoietin level is higher than 500 U per liter, administering recombinant erythropoietin may be of little help. There are many exceptions, however, and because even a slight increase in red cell production may render some patients transfusion-independent, it seems reasonable to conduct a therapeutic trial. Such a trial should consist of giving 10,000 units three times a week subcutaneously. If no appreciable increase in hemoglobin concentration or decrease in transfusion requirements occurs, augmentation of the dose is probably of little benefit. This questionable benefit of recombinant erythropoietin therapy in patients with nonrenal anemia stands in stark contrast to its predictable benefit for patients with anemia due to kidney failure, and that in itself may be enough of an accomplishment.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Acid-Base Disorders Revisited

To the Editor: The diagnosis and treatment of acid-base disturbances constitute a crucial part of the practice of medicine. Learning these concepts has been notoriously difficult in most medical schools, including ours. For this reason, the article by Haber in the August 1991 issue evoked a considerable amount of interest and enthusiasm.[1] Simplifying the approach to acid-base disturbances to only three steps without memorizing rules of "compensation" or using a nomogram seems at first glance to be extremely appealing.

On further evaluation, however, there are some problems with this approach. Consider the case of a patient who has a metabolic acidosis and inadequate respiratory adaptation. The arterial blood gas values might be

$$pH = 6.82,\ HCO_3^- = 6 \text{ mmol/liter},\ P_{CO_2} = 38 \text{ mm of mercury.}$$

Clearly this acid-base disturbance is clinically best viewed as a complex acid-base disturbance. Such a patient might, in fact, require intubation and assisted ventilation. Using Haber's algorithm, however, the importance of the inadequate respiratory compensation, which could have profound clinical implications, would be missed.

Therefore, we suggest that "rules of compensation," although tedious and difficult to memorize, play an important role in the clinical evaluation of acid-base disturbances, mandating the addition of another "step" to Haber's "rules of thumb."

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Dr Haber Responds

To the Editor: Carson and Shapiro are concerned that a simplified approach to acid-base analysis may miss important disorders of compensation. Quantitative analysis remains the standard for assessing acid-base status, but a less complex approach can provide much of the same information.

Consider the example offered by Carson and Shapiro. The low pH and low bicarbonate concentration indicate a metabolic acidosis is present; the normal P_{CO_2} indicates respiratory compensation has not occurred. Because the respiratory response to changes in pH is rapid, a normal P_{CO_2} in the presence of a severe metabolic disturbance is inappropriate and indicates that an additional respiratory disorder has prevented the normal compensatory response. Recognition of the mixed nature of this acid-base disturbance does not require a quantitative approach but merely knowledge of the direction and time course of normal respiratory compensation and an assessment of whether or not it has occurred.

A similar approach can be applied to metabolic compensation. Because metabolic compensation requires renal adjustment and takes three to five days, the absence of metabolic compensation for a respiratory disorder indicates that the respiratory disturbance is acute. Evidence of metabolic adjustment points to a more chronic disorder.

These guidelines can be expressed in behavioral terms: Whenever a primary acid-base disorder is identified, determine whether compensation has occurred. If respiratory compensation is expected, but not observed, then an additional respiratory disorder is present. If metabolic compensation is expected but not observed, then the primary respiratory disorder is acute. This approach will identify most clinically important disorders of compensation, including those in the example posed by Carson and Shapiro, without memorizing "rules of compensation" or using a nomogram.

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Manifestations of Adult Varicella in the United States Navy, 1984-1987

To the Editor: Varicella zoster virus (VZV) infection remains a significant cause of hospital admissions and lost workdays in the US Navy. A review of military cases sheds new light on complication rates of this disorder.

We reviewed the medical records of patients with VZV infection admitted to Naval Hospital, San Diego between January 1984 and April 1987. The diagnosis was made on clinical grounds alone. All radiographs were reviewed and were classified as abnormal if two pulmonologists independently agreed that signs of pneumonitis were present. The

TABLE 1.—*Ethnic Background of Patients With Varicella (n = 485)*

Race	Patients No.	Patients (%)
White	252	(52.0)
African American	110	(23.0)
Filipino	86	(18.0)
Hispanic	12	(2.5)
Asian	10	(2.1)
Unrecorded	15	(2.4)

records of immunocompromised patients were excluded from analysis.

A total of 485 charts were reviewed: 460 men and 25 women, ages 17 to 49 years (median 21). Mean hospital stay was 7 days (1 to 18 days). Patients' ethnic backgrounds are summarized in Table 1. A total of 325 patients had complete blood counts done, 214 had liver function tests, 236 had urinalyses, and 268 had chest radiographs. The primary care physicians determined which studies were done. Complications consisted of the following: thrombocytopenia (platelet count $< 150 \times 10^9$ per liter [150×10^3 per μl]), hepatitis (alanine or aspartate aminotransferase levels $> 2 \times$ normal), abnormal urinary sediment (erythrocytes > 10 per high-power field, $>2+$ protein, or leukocytes > 8 per high-power field), pneumonia (infiltrate on chest x-ray film), pyoderma, conjunctivitis, and nondermal superinfections. Table 2 shows a breakdown of complications.

TABLE 2.—*Percentage Breakdown of Complications Occurring in Adults With Varicella (n=485)*

Complication	Patients: No./Cases of Varicella	Patients: (%)
Pneumonia	12/268*	(4.5)
Pyoderma	13/485	(2.7)
Nondermal superinfections	20/485	(4.1)
Thrombocytopenia	50/325	(15.4)
Abnormal liver function tests	84/214	(39.2)
Abnormal urinary sediment	41/236	(17.4)
Conjunctivitis	9/485	(1.8)

*Cases with radiographs.

Demographics

Race. Comparison with 1983 personnel records demonstrates that a disproportionate number of patients in the present study were Asian or Filipino (20% of cases versus <2% of active-duty personnel). This is likely due to the higher incidence of adult varicella in persons from semitropical countries.[1]

Sex. Women constitute between 8% and 10% of naval personnel but only 5.1% of cases. This finding may be explained by the lower ratio of women in certain racial groups (<3% of active-duty Filipinos are women).

Clinical Features

Most patients could not relate a contact history and presented with mild constitutional complaints, fever, and a typical skin rash. Only 10% reported cough, but many complained of upper respiratory tract symptoms, predominantly sore throat. On admission, fever was noted in 72%.

Hematologic Abnormalities

In previous reviews, thrombocytopenia was seen predominantly in children with severe disease.[2,3] In our review, mild thrombocytopenia occurred in 15.4% of patients, with no bleeding complications. The mechanism for thrombocytopenia is postulated to be shortened platelet survival due to immunologic sensitization.[4]

Hepatitis

A total of 39.2% of the patients had elevations in serum aminotransferase levels—as much as six times the upper limit of normal. Other causes for aminotransferase elevations were not demonstrated (including hepatitis A and B serologic tests or Monospot tests), and levels returned to normal on subsequent testing. Previous studies have found subclinical hepatitis occurring in 25% to 77% of varicella cases in children and young adults.[5,6]

Abnormal Urinalysis

A total of 17.4% of the urinalyses were found to be abnormal. Urine cultures were without growth, and no gross abnormalities of renal function occurred (normal blood urea nitrogen and creatinine levels). Hematuria and proteinuria have been described only rarely in patients with varicella and were attributed to "nephritis."[7] Isolated proteinuria could be explained by fever, stress, or dehydration, but in patients with hematuria, pyuria, or both (32% of abnormal urinalyses), subclinical renal or visceral (bladder or urethral) injury was likely.

Pneumonia

Only 12 radiographs (4.5%) showed abnormalities consistent with pneumonia. This is considerably less than the generally accepted incidence of 15% to 20%.[8] Clinical manifestations were mild, with cough being a poor predictor of pneumonia (55% sensitivity and 92% specificity in patients with radiographs). All 12 patients had normal lung examinations.

Though our review is limited by being retrospective without a standardized collection of laboratory studies, it demonstrates the multiorgan involvement of varicella infection. Urinary abnormalities, thrombocytopenia, and aminotransferase elevations were common. Radiographic evidence of pneumonia occurred in only 4.5% and did not correlate well with patients' signs or symptoms. Even if radiographs had been obtained on all patients, it is unlikely that our incidence of pneumonia would have approached those reported previously. Though disease manifestations were generally mild, the significant morbidity, lost workdays, and the unique problem with contagious risk in military personnel warrant trials of antiviral therapy and VZV vaccines.

The Chief, Navy Bureau of Medicine and Surgery, Washington, DC, Clinical Investigation Program #87-16-2288-00 sponsored this study. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

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Successful Treatment of Markedly Symptomatic Patients With Type II Diabetes Mellitus Using High Doses of Sulfonylurea Agents

To the Editor: Markedly symptomatic patients with type II diabetes mellitus—with pronounced polyuria, polydipsia, polyphagia, and weight loss—are usually admitted to hospital to be treated with insulin, regardless of the potential for outpatient instruction. We report the successful outpatient treatment of these patients with high doses of sulfonylurea agents.

Asymptomatic or mildly symptomatic patients with type II diabetes are initially treated with an appropriate diet for at least a month. If one- or two-hour postprandial glucose levels remain above 10 mmol per liter, small amounts of a sulfonylurea agent are introduced and gradually increased every two to four weeks until satisfactory control is obtained. In contrast, markedly symptomatic type II diabetic patients receive the highest possible dose of one of the four most effective sulfonylurea agents (tolazamide, chlorpropamide, glyburide, or glipizide) and are monitored frequently (twice a week for the first week, weekly for the next three weeks, and then monthly). Patients older than 65 receive half this dose (and are not prescribed chlorpropamide), which is increased quickly to the highest possible dose within two weeks if they do not respond satisfactorily. When treatment is effective, symptoms abate within several days and often disappear completely after the first week, certainly by two weeks.

Fourteen patients fulfilled our criteria for markedly symptomatic type II diabetes with pronounced polyuria, polydipsia, nocturia, and short-term weight loss over weeks to several months, ranging as much as 12 kg (26 lb). Mild

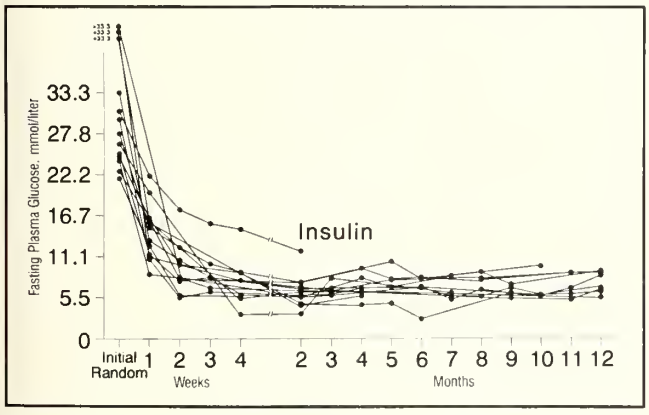

Figure 1.—Initial random plasma glucose concentrations before and fasting plasma glucose concentrations after receiving maximal doses of a sulfonylurea agent are shown in 14 markedly symptomatic patients with type II diabetes mellitus.

ketonuria was present in some, but serum bicarbonate levels were normal. None had altered mental status at the time of presentation nor evidence of severe intravascular volume depletion as assessed by the measurement of orthostatic blood pressure and pulse. All of the patients were considered to be reliable and capable of following the instructions necessary for their care. The seriousness of the situation and the potential for their hyperglycemia to worsen if the sulfonylurea agent therapy did not work (or type I diabetes eventually developed) was stressed with every patient. There were ten men and four women whose ages (years) and body mass indices (kg per m^2) ranged from 28 to 65 and 22.6 to 49.8, respectively. Their initial random plasma glucose levels all exceeded 22 mmol per liter, with nine between 22 and 30 mmol per liter and five over 30 mmol per liter. All but two had newly diagnosed diabetes; one was receiving 5 mg of glipizide, and one was treated by diet. A precipitating event such as infection could not be identified in any of the patients. Eleven patients were given a maximum dose of glyburide (20 mg per day in divided doses); two patients older than 65 were started on a regimen of 10 mg per day of glyburide, which

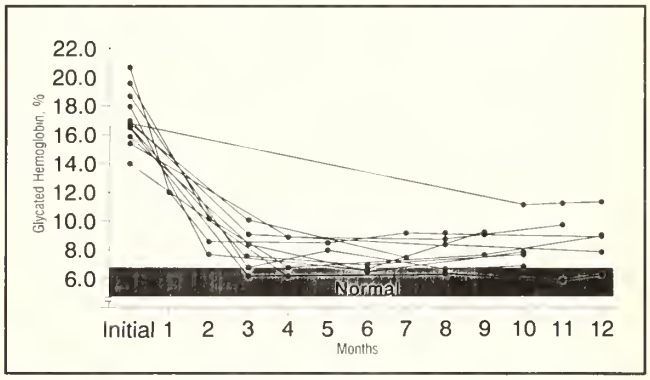

Figure 2.—Glycated hemoglobin levels are shown in 12 markedly symptomatic patients with type II diabetes before (initial) and after receiving maximal doses of a sulfonylurea agent.

was increased to 15 mg per day within two weeks before a satisfactory response was seen; one patient was initially treated with 750 mg per day of chlorpropamide.

The individual responses of the 14 patients are shown in Figure 1 (fasting plasma glucose concentrations) and Figure 2 (glycated hemoglobin levels). Glycated hemoglobin levels were not measured in one patient at all and not before insulin therapy was started in the only one who required it. The initial glycated hemoglobin levels, all above 14% and most above 16%, indicated that the patients had been extremely hyperglycemic for at least two months. Of the 14 patients, 13 responded satisfactorily. The fasting plasma glucose concentrations decreased notably by two weeks in most patients. The improvement was sustained for as long as a year (arbitrary cutoff point for this report) in those who remained in their health maintenance organization or until we were unable to see them because they changed or lost their medical insurance. At these times, five patients were taking no sulfonylurea agents, one was receiving 125 mg of acetohexamide, and the rest were taking submaximal daily amounts of glyburide as follows: 2.5 mg (2 patients); 5 mg (2 patients); 10 mg (2 patients); and 12.5 mg (1 patient). One patient failed to meet our criteria for a successful response (fasting plasma glucose < 10 mmol per liter), and insulin therapy was started two months after the patient's first visit.

Body weight was not an important factor. Both thin and obese patients responded. Furthermore, weight loss did not account for the successful response. The average weight of the 13 patients who responded was 95.4 kg (210 lb). The average final weight of the seven patients in whom this information was available was 94.1 kg (207 lb), an increase of 3 kg (6.6 lb) in this subset.

There is no consensus regarding the initial treatment of patients with type II diabetes who have marked hyperglycemia.[1-3] In asymptomatic patients, especially older, obese ones, sulfonylurea agents seem to be the drug of choice

whereas in younger, lean patients, insulin seems to be favored.[1-3] Insulin therapy is usually recommended for symptomatic patients with weight loss.[3] Initiating insulin therapy is time-consuming, leads to profound changes in a patient's life-style, and, in many locales, requires hospital admission. For these reasons, a trial of maximal doses (half maximal in patients older than 65) of sulfonylurea agents was tried in markedly symptomatic patients with type II diabetes to determine whether a satisfactory response could be quickly achieved and insulin therapy avoided. This was successful in 13 of 14 patients. If insulin therapy is eventually deemed necessary, it can be started more gradually in an outpatient setting.

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Lessons From the Practice

Clinical Note—Doctor-Patient Bonding

RALPH CRAWSHAW, MD, *Portland, Oregon*

Personal illness has a way of sharpening the clinical acuity of physicians. At least it did for me, a psychiatrist, recently recovered from a severe fever of undetermined origin. The experience taught me more about doctor-patient bonding than I had ever expected to know.

The fever, a vicious affair, repeatedly spiked at 102.8°F while the immature forms of my leukocytes "banded" at a 60% rate. As my condition worsened, treatment at a local teaching hospital became imperative.

I had just returned from the Marquesas Islands, and though I never convinced the medical staff, I thought I had dengue fever. Granted my medical history was a bit unusual, yet I was surprised and finally peeved at having to repeat it at least eight times. As it turns out, the business of repeating a medical history numerous times may not be unusual. In fact, repetition may be a necessary ingredient for developing an enduring doctor-patient relationship.

Initially I gave a detailed history to my physician in his office. He listened attentively and, once he was convinced I needed to be admitted to hospital, called the admissions office and relayed my history to expedite my path to a hospital bed. When I arrived at the hospital, I gave all the ritual numbers of birth, insurance, and customary personal whereabouts to the admissions office. Then I was asked what eventually became a litany: "In your own words, would you tell me about your condition from the time you first noticed something wrong?" I did, only to repeat the process again with the admitting nurse, the charge nurse, the intern, the resident, the visiting exchange resident, various attending physicians, the chief of the Infectious Diseases Service, and the chief of Medicine.

It was not easy to report my medical history over and over. Given my murky sensorium, after a few repetitions the details tended to run together and blur, leaving a sense of not having it right. Repetition of the facts generated new facts demanding to be integrated into the elaborated account. No patient wishes to appear inconsistent or, worse, confused. Knowing any inconsistency could stir the interrogators to more questions, including a request to repeat it all again from the beginning, I tried, as best I could, to settle for a standard form.

One interrogator pressed for the precise time of onset, a detail that failed to interest the next, who was preoccupied with the exact site of my headaches. Neither of these points interested the third interrogator, who encouraged me to enlarge in detail on past reactions to fevers. Finally, simmering with fever and unable to concentrate, my only wish was for an end to the questioning.

As the fever subsided, my mind cleared, and during my convalescence the obvious emerged. Those asking for a personal account of my misery all bore clinical responsibility for my care. I realized they consistently did two things: First, each asked me to relate the story of my present illness firsthand, and then each touched me. Initially I attributed their need for a personally recounted history to some hidden concern about hearsay or inaccurate information, but given the overwhelming duplication of facts on the chart and in their consultations, fear of misinformation could not be it. Finally, as I came to see it, the need for my repeating my history was part of a professional ritual, the process of establishing a relationship with me.

My interrogators requested my version of why I was in the hospital in order for me "to be," in order for them to hear "me." Albeit unconsciously, they were developing their personal data bank as a necessary part of the process of converting me from a case into their patient. My account was a necessary part of becoming their patient. Without my personal contribution, I would remain nothing more than an interesting diagnostic challenge. Without my personal account, there could be no emotional bond between me and my physician.

The other unfailing action of these physicians was to touch me. A few, unhesitatingly and without introduction, reached out and took my hand. Some palpated my aching limbs, others pressed my nailbeds, but all involved in my care, nurses included, never failed to touch me. It was as if they were sealing the bond by touching the patient.

While my immediate reflections about physicians' behaviors ceased with the return of health, the various ways they bond with their patients remain an open and interesting consideration for me. No matter the specialty, my experience with the doctor-patient relationship as a patient has led me to expect a sustained, caring commitment from my physician.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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(Crawshaw R: Clinical note—Doctor-patient bonding. West J Med 1992 Aug; 157:201)

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Lessons From the Practice

Victor

HARLAND GOLDWATER, MD, *Santa Barbara, California*

Victor was already in his mid-80s when he was brought to me by his wife and daughter. He had been a Danish champion boxer in his early days and then had become a sea captain serving the United States government during wartime. He spoke Danish, English, and Spanish fluently and was the kind of upbeat person most people enjoy. Over about a five-year period, his infirmity increased slowly, and he followed the common route from wheelchair to bed.

I attended his medical needs every month by calling on him at his residence. Later, he was in a home where he was one of two people being cared for by a fine Greek lady. They got along well, but Victor started to lose contact with others for days or weeks at a time, and then, suddenly, he would be able to make coherent and relevant remarks again. He was always kind and as cheerful as anyone could be under those circumstances.

One day, the Greek lady called to say that she thought Victor was dying and asked me to come over.

Victor was neatly tucked in bed, and the room was clean and pleasant. He opened his eyes after I had stood there for a moment, and I said hello. He responded appropriately in Spanish, and I surmised that he was in a good mood and connected to the real world again.

I checked him over and then simply asked him if there was anything that I could do for him. There was a very long pause, and I thought maybe he had slipped out of touch again. But that was not the case.

Victor turned his head, looked squarely at me, and slowly and distinctly said in English, "Take very good care of yourself!"

In his dying hours, Victor turned the tables on me and concerned himself with my well-being and future. I believe Victor liked me as I did him, and, when he knew there was nothing more that could be done for him, he responded very much like a loving parent. He gave the best advice this physician has ever received.

I took Victor's advice and better controlled my hours and activities. Then, about five years afterward, having completed 35 years of general practice, I turned my patients over to another physician and started a long sabbatical. Mine is not a retirement in the absolute sense—I have been doing locum tenens in Native American clinics in California and truly enjoying the experience. I am able to balance the time for family, recreation, and profession.

All this may have come about without Victor's advice, but his were not idle words.

* * *

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(Goldwater H: Victor. West J Med 1992 Aug; 157:202)

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OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

DERMATOLOGIST. Immediate opportunity available for full- or part-time position with University affiliated multispecialty group in one of the most desirable cities. We offer a balanced lifestyle, competitive salary and an excellent benefit package. Send CV to Mary Anderson, Personnel Representative, Pacific Medical Center, 1200 12th Ave S., Seattle, WA 98144; (206) 326-4111.

CALIFORNIA MULTISPECIALTY. Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians in Los Angeles suburb to join 100 member multispecialty medical group. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center—5, 17821 S. Pioneer Blvd, Artesia, CA 90701.

OB/GYN—Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE Physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

ESCAPE those urban hassles and come to scenic northern California, southern California, and Phoenix, Arizona. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Mark Oswald of Gielow/Laske Associates, Inc, 306 N Milwaukee St, Milwaukee, WI 53202; (800) 969-7715, FAX (414) 226-4131. Confidential inquiries welcome.

BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BE/BC, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273.

BE/BC FAMILY PRACTITIONER to join one Family Nurse Practitioner, one Pediatric Nurse Practitioner and one OB/GYN Nurse Practitioner, and two part-time OB/GYNs in Walla Walla, Washington. Share call with four practitioners. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate Loan Repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

PEDIATRICIANS—Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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SAN FRANCISCO BAY AREA. Two physician (with two physician assistants) General Practice/Family Practice group seeks BC/BE Family Practice, Internal Medicine, or Emergency Medicine practitioner capable of General Practice, to join thriving practice in rapidly growing Tri-Valley area 40 minutes east of San Francisco. No Obstetrics. Historic wine country; sophisticated professional and suburban patient base. Competitive salary first year, with bonus potential; consideration for partnership thereafter. Will also consider minimum one year employment contract not leading to partnership. Congenial atmosphere, attractive surroundings. Excellent financial opportunity in beautiful area. Send CV to James A. Blackwell, MD, Livermore Medical Clinic, 87 Fenton St, Ste 210, Livermore, CA 94550.

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BC/BE OB/GYN to join one Internist, one Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs. Competitive salary, excellent benefit package, including vacation up to 32 days per year and professional liability. Public Health Service immediate loan repayment slot. Contact Sylvia Arroyo, Clinic Administrator, Family Medical Center, PO Box 515, Walla Walla, WA 99362; (509) 525-6650, or Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant; (509) 865-5898.

INTERNAL MEDICINE—Southern California. Challenging career opportunities for specialists in Internal Medicine desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PRIMARY CARE PHYSICIAN wanted for expanding eastern Washington clinic. Full- and part-time positions available. Located in prime recreational area. Skiing, sailing, fishing, hunting all within a short distance. Enjoy mild climate, excellent schools and a major university branch campus in growing community of 100,000 plus. Challenging work in a superbly equipped clinic with state-of-the-art lab, x-ray, laser, and endoscopy. Above average compensation and benefits including malpractice, health insurance, and CME. Contact Dr Stephen L. Smith, 310 Torbett, Richland, WA 99352; (509) 545-8340 or FAX (509) 946-7666.

PEDIATRICIANS—NEVADA, CALIFORNIA, TEXAS! Private practice opportunities available. Hospital sponsored with coverage or join an established group. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Ft Worth, TX 76185, or FAX (817) 927-0030.

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SOUTHERN CALIFORNIA. Family Practice physician position available in Riverside County. Guaranteed income, excellent benefits with early partnership. Send résumé to Number 265, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS POSITIONS. VA Clinic/VAMC ER vacancy exists at the Salt Lake City VAMC satellite outpatient clinic at Pocatello, Idaho for BE/BC Family Physician or a BE/BC General Internist. Scenic mid-size college town with all the advantages of rural living. This clinic sees patients by appointment only, Monday through Friday, 8:30-5:00 p.m. Vacancy also exists at the Salt Lake City VAMC admitting office for BE/BC Emergency, Internal Medicine, or Family Practice physician. The VA offers a wide range of benefits. For more information and application contact Glenda Taylor, Personnel, (801) 582-1565, ext 1284. Base salary and special pay based on qualifications. Position subject to drug screening. The VA is an equal opportunity employer.

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SEATTLE, WASHINGTON. FAMILY PHYSICIAN BC/BE, part- or full-time, wanted for a stimulating practice in a comprehensive Primary Care community clinic serving a diverse Asian/Pacific Islander population. OB required. Cantonese language skills helpful. Contact Debra Cavinta, Administrative Assistant, International District Community Health Center, 416 Maynard Ave S, Seattle, WA 98104; (206) 461-3617. EOE. Closing Date 9/30/92.

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BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

CALIFORNIA CENTRAL COAST. Young BC Family Practitioner desires same to share booming practice. Dr Okerblom, 1145 E Clark Ave, Orcutt, CA 93455.

TWO BC/BE OB/GYN'S with commitment to caring for the underserved, needed to join Primary Care (OB, Family Practice, Pediatrics, Internal Medicine), community health clinics in Toppenish and Grandview, Washington. Rural setting, beautiful sunny central Washington near Columbia River gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

AMBULATORY CARE, Hayward, Modesto, Orange County, California. Thriving practices, attractive facilities, competitive salary, profit-sharing, partnership with growth potential. Contact John Gravette, California Emergency Physicians, 2101 Webster St, #1050, Oakland, CA 94612; (510) 835-7431. Outside of California, (800) 842-2619.

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

(Continued on Page 207)

(Continued from Page 206)

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Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

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GILROY, CALIFORNIA. BC INTERNIST to join established but growing private practice in Gilroy, California. Ideal candidate will have one to two years practice experience. Guaranteed salary and benefits. Excellent practice opportunity in this growing community. Send CV to Number 272, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PALO ALTO MEDICAL CLINIC, a 150 physician multispecialty group with a national reputation for innovation and excellence, seeks BC Family Practice or Emergency Medicine physicians for full-time practice in Urgent Care facility. Occupational Medicine experience desirable. Competitive salary based on experience. Excellent benefits package. Two year partnership track. Please forward letter of interest and CV to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

SEATTLE. As the result of population growth and reputation, this 28 physician group practice is in need of several recently trained Family Practitioners. This suburban community is situated within minutes of downtown Seattle and within one hour of Mt. Rainier. Remuneration package includes base salary plus incentive and full benefits with partnership after two years. Call rotation every 7th night and weekend. Congenial atmosphere. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

SOUTHERN CALIFORNIA. Family Practitioner needed by 20 physician Primary Care group. Several requirements have created opportunity for future partner. Generous salary and benefit package in return for commitment to quality. Location is 45 minutes east of beaches. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

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FAMILY PRACTICE POSITIONS available in the northern California (north bay area) and southern California (Palm Springs and Los Angeles); affiliated with local hospitals; malpractice paid, excellent benefits and compensation. If interested, please call IMN (800) 775-4677.

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- Internal Medicine/ Gastroenterology
- General Surgery

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(Continued on Page 209)

(Continued from Page 208)

NORTHERN CALIFORNIA

Positions available for BC/BE OB/GYNs with private group practices in San Francisco, SF Peninsula, Marin County, San Jose, and Sacramento; with multispecialty groups in South Bay. For information about these opportunities, please call **Mary Letterii** at **(800) 229-0411** or **(415) 399-8840** or send your CV to **Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111, FAX (415) 399-0411.** You can depend on us to handle your inquiry with complete confidence.

PEDIATRICIAN—SANTA MONICA. Associate needed for rapid takeover of busy, lucrative Pediatric practice. Good coverage weekends. Low overhead. Rare opportunity. Phone Lisa; (310) 829-1752 for details.

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NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through Fall of 1994. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD, EOE/M/F/V/H.

NEVADA—GASTROENTEROLOGIST. BC/BE needed to join General Intern practice in southern Nevada. Generous salary leading to full partnership. Interest in Internal Medicine preferred. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

BE/BC PHYSICIANS. Moreno Valley Medical Group. General Practitioner, OB/GYN, Internal Medicine. Excellent compensation. Send CV to Moreno Valley Medical Group, 22810 Alessandro Blvd, Moreno Valley, CA 92388. Call (714) 653-2500 (Marcel).

OB/GYN POSITIONS and outpatient GYN positions available in northern (north bay) and southern California (Los Angeles and San Diego); malpractice paid, excellent benefits. Call IMN, (800) 775-4677.

DERMATOLOGY. BC/BE Dermatologist needed for busy Medical/Surgical practice. Located in wonderful recreational area on California's beautiful central coast. Ideal location for families, close to lake, ocean, university campus. Surgical and/or pathology skills preferred. Partnership potential. Send résumé to Number 268, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PULMONARY/CRITICAL CARE. Immediate opening for BC/BE Pulmonologist to join two BC Pulmonologists/Intensivists in expanding practice located in a desirable southern California seaside community. This outstanding opportunity provides a 100% Pulmonary/Critical Care consultative practice, academic affiliations/teaching position available locally. Please reply with a letter of introduction and CV to Number 269, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 210)

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(Continued from Page 209)

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(Continued on Page 211)

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1993, date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-13, 1992, Copper Mountain.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1992, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 30-August 1, 1992, Coeur d'Alene.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1992, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1993, date and place to be announced.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1993, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. September 16-19, 1992, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: October 1-4, 1992, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1993, date and place to be announced.

ADVERTISING INDEX

THE AMERICAN ACADEMY OF FAMILY PHYSICIANS 115

AMERICAN MEDICAL WOMEN'S ASSOCIATION 117

CIGNA HEALTHPLAN 207, 209

CLASSIFIED ADVERTISING 203, 204, 205, 206, 207, 208, 209, 210, 211

COMP HEALTH 206

DOMUS MEDICAL MANAGEMENT 127

ELI LILLY & COMPANY
Humulin ..... 2nd Cover

FHP HEALTH CARE 209

GYN CME FUND INC. 121

HOFFMANN LA ROCHE INC.
Valium ..... 3rd & 4th Covers

JOURNAL WATCH 129

KAISER PERMANENTE 206

MARION MERRELL DOW
Cardizem 123, 124

PALISADES PHARMACEUTICALS INC.
Yocon 119

G.D. SEARLE & COMPANY
Calan SR 111

SMITHKLINE BEECHAM PHARMACEUTICALS
Tagamet 131, 132

SOUTHERN CALIFORNIA PHYSICIANS INSURANCE EXCHANGE 107

SUTTER NEUROSCIENCE CENTER 109

US AIR FORCE 205

US ARMY RESERVE 113

VOICE CARE SYMPOSIUM 127

THE WESTERN JOURNAL OF MEDICINE
Special Issues 128
Cross-cultural Medicine—A Decade Later 130
Subscription 131

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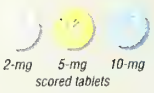

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INDICATIONS AND USAGE
ROGAINE is indicated for treatment of androgenetic alopecia, expressed in men as male pattern baldness of the vertex and in females as diffuse hair loss or thinning of the frontoparietal areas. At least 4 months of twice daily applications are necessary before evidence of hair growth can be expected

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol, or ethanol

WARNINGS
1. Need for normal scalp Before starting treatment, make sure that the patient has a normal, healthy scalp Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
2. Potential adverse effects: Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, or unusual sensitivity could, at least theoretically, produce a systemic effect

Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN® Tablets for details)
– salt and water retention, generalized and local edema
– pericardial effusion, pericarditis, tamponade
– tachycardia
– increased incidence of angina or new onset of angina

Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects. Additive effects could also emerge in patients being treated for hypertension.

Potential patients should have a history and physical and should be advised of potential risks A risk/benefit decision should be made Heart patients should realize that adverse effects may be especially serious

Alert patients to the possibility of tachycardia and fluid retention and monitor for increased heart rate, weight gain, or other systemic effects

PRECAUTIONS
General Precautions. Monitor patients 1 month after starting ROGAINE and at least every 6 months thereafter Discontinue ROGAINE if systemic effects occur

The alcohol base will burn and irritate the eye. If ROGAINE reaches sensitive surfaces (eg, eyes, abraded skin, and mucous membranes), bathe with copious cool water

Avoid inhaling the spray

Do not use in conjunction with other topical agents, such as corticosteroids, retinoids and petrolatum, or agents that enhance percutaneous absorption

ROGAINE is for topical use only Each mL contains 20 mg minoxidil, and accidental ingestion could cause adverse systemic effects

Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis, or severe sunburn, may increase minoxidil absorption
Patient Information. A patient information leaflet is included with each package and in the full product information
Drug Interactions. No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine.
Carcinogenesis, Mutagenesis, and Impairment of Fertility: No carcinogenicity was found with topical application. Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate.
Pregnancy Category C: ROGAINE should not be used by pregnant women.
Labor and Delivery. The effects are not known.
Nursing Mothers. ROGAINE should not be administered to nursing mothers
Pediatric Use: Safety and effectiveness has not been established for patients under age 18
Postmenopausal Use: Efficacy in postmenopausal women has not been studied

ADVERSE REACTIONS
ROGAINE was used by 3,857 patients (347 females) in placebo-controlled trials. Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients

Dermatologic: irritant or allergic contact dermatitis – 7 36%, **Respiratory:** bronchitis, upper respiratory infection, sinusitis – 7.16%, **Gastrointestinal:** diarrhea, nausea, vomiting – 4.33%, **Neurologic:** headache, dizziness, faintness, light-headedness – 3 42%; **Musculoskeletal:** fractures, back pain, tendinitis – 2 59%; **Cardiovascular:** edema, chest pain, blood pressure increases/decreases, palpitations, pulse rate increases/decreases – 1.53%; **Allergic:** nonspecific allergic reactions, hives, allergic rhinitis, facial swelling, sensitivity – 1 27%, **Metabolic-Nutritional:** edema, weight gain – 1.24%; **Special Senses:** conjunctivitis, ear infections, vertigo – 1 17%, **Genital Tract:** prostatitis, epididymitis, vaginitis, vulvitis, vaginal discharge/itching – 0 91%; **Urinary Tract:** urinary tract infections, renal calculi, urethritis – 0.93%; **Endocrine:** 0 47%, **Psychiatric:** anxiety, depression, fatigue – 0.36%; **Hematologic:** lymphadenopathy, thrombocytopenia – 0 31%.

Patients have been followed for up to 5 years, and there has been no change in incidence or severity of reported reactions Additional events have been reported since marketing and include eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking; sexual dysfunction; visual disturbances, including decreased visual acuity, exacerbation of hair loss, and alopecia.

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application. 1 mL should be applied to the total affected areas twice daily Total daily dose should not exceed 2 mL. If the fingertips are used to facilitate drug application, wash the hands afterwards If hair regrowth is realized, maintenance of twice daily applications is necessary for additional and continued hair regrowth

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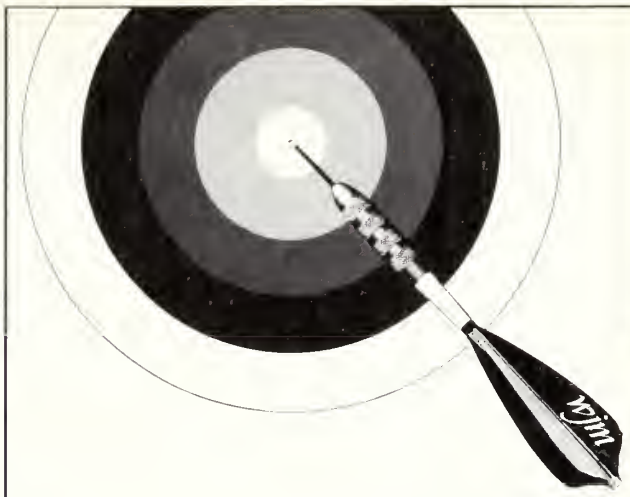

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The Western Journal of Medicine

VOLUME 157 • NUMBER 3 • SEPTEMBER 1992

CONTENTS

Cross-cultural Medicine
A Decade Later

JUDITH C. BARKER, PhD, *Special Editor*
M. MARGARET CLARK, PhD, *Consulting Editor*

This special issue was funded in part by a Henry J. Kaiser Foundation grant.

247 **Beyond Words**
LINDA HAWES CLEVER, MD

248 **Cultural Diversity—Changing the Context of Medical Practice**
JUDITH C. BARKER, PhD
Dr Barker, the special editor for this issue, is with the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco.

255 **Translation Is Not Enough—Interpreting in a Medical Setting**
LINDA HAFFNER
From Community and Patient Relations, Stanford University Medical Center, Stanford, California.

260 **Modesty, Sexuality, and Breast Health in Chinese-American Women**
BERTHA MO, PhD, MPH
From the Consultation, Education, and Information Unit, Division of Mental Health and Substance Abuse, Department of Public Health, San Francisco, California.

265 **Health, Illness, and Immigration—East Indians in the United States**
JAYASHREE RAMAKRISHNA, PhD, MPH, and MITCHELL G. WEISS, MD, PhD
From the Department of Health Education, National Institute of Mental Health and Neuro Sciences, Bangalore, India, and the Departments of Social Medicine and Psychiatry, Harvard Medical School, Boston, and Cambridge Hospital, Cambridge, Massachusetts.

271 **Health Issues of Afghan Refugees in California**
JULIENE G. LIPSON, RN, PhD, and PATRICIA A. OMIDIAN, MA
From the Department of Mental Health, Community and Administrative Nursing, School of Nursing, and the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco.

276 **Gypsies and Health Care**
ANNE SUTHERLAND, PhD
From the Department of Anthropology, Macalester College, St Paul, Minnesota.

281 **Health and Aging of Urban American Indians**
B. JOSEA KRAMER, PhD
From the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco, and the County of Los Angeles Department of Community and Senior Citizens Services, Los Angeles, California.

(Continued on Page 224)

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References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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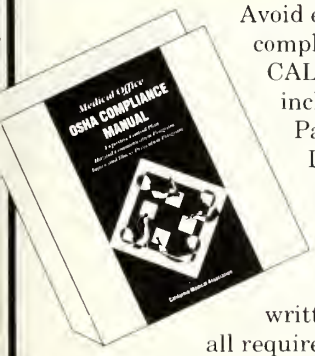

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Vaughn A. Starnes, M.D. has joined the University of Southern California School Medicine.

Vaughn A. Starnes, M.D., has joined the Universit Southern California School of Medicine as Professo Surgery, Chief of the Division of Cardiothoracic Su and Director of the USC Cardiothoracic Center at University Hospital, Childrens Hospital Los Angeles and Angeles County+USC Medical Center. Dr. Starnes is a w recognized leader and innovator in adult and pediatric h heart-lung and lung transplantation and treatment of conge heart disease.

In 1984 Dr. Starnes was accepted to the Stanford Cardiot cic program, where he completed two years as a resident in ca vascular surgery, and one year as chief resident in car transplantation under the guidance of Norman Shumway, M.

In 1988 Dr. Starnes was appointed director of Stanford's h lung transplantation program, and later became chief of pedi heart surgery and director of the transplant program at Stan Lucile Salter Packard Childrens Hospital. He performed about adult and pediatric cardiac cases annually at Stanford. In add to his adult cardiothoracic surgical expertise, Dr. Starnes earn national reputation for his work in pediatrics.

Dr. Starnes also pioneered lung and heart-lung transplant cedures in children that previously had only been performe adults. In 1991 he was the first surgeon to transplant the upper lobe of a 2-year-old donor into a newborn with pulmo hypertension who could not be weaned off ECMO (Extracorp Membrane Oxygenation). In 1992, he performed the first transplant on a baby with congenital diaphragmatic hernia

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(Continued from Page 218)

286 **African-American Culture and AIDS Prevention—From Barrier to Ally**
BENJAMIN P. BOWSER, PhD
From the Department of Sociology and Social Services, School of Arts, Letters, and Social Sciences, California State University, Hayward.

290 **Mental Health and Illness in Vietnamese Refugees**
STEVEN J. GOLD, PhD
From the Department of Sociology, Whittier College, Whittier, California.

295 **Dysphoria and Somatization in Iranian Culture**
KAREN L. PLISKIN, PhD
From the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco.

301 **Working With Refugee Survivors of Torture**
BARBARA CHESTER, PhD, and NEAL HOLTAN, MPH
From the Hopi Foundation, Tucson, Arizona, and the Department of Medicine, Ramsey Clinic and University of Minnesota Medical School, Minneapolis.

305 **This, That, and the Other—Managing Illness in a First-Generation Korean-American Family**
SOO-YOUNG CHIN, PhD
From the Departments of Anthropology and Asian American Studies, College of Social Sciences, San Jose State University, San Jose, California.

310 **Use of Traditional and Modern Health Services by Laotian Refugees**
STUART C. GILMAN, MD, MPH; JUDITH JUSTICE, PhD, MPH; KAOTA SAEPHARN; and GERALD CHARLES, MD
From the Regional Medical Education Center and Western Region Special Studies Group, Veterans Affairs Medical Center, Long Beach; the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco; the Ethnic, Asian-American Studies, Center for Southeast Asian Studies, University of California, Berkeley; and the Medical Service, VA Medical Center, San Francisco, California.

316 **The Effect of Values and Culture on Life-Support Decisions**
JILL KLESSIG, MD
From the Department of Medicine, University of California, Los Angeles, School of Medicine, Olive View Medical Center, Los Angeles, and the Department of Veterans Affairs Medical Center, Sepulveda, California.

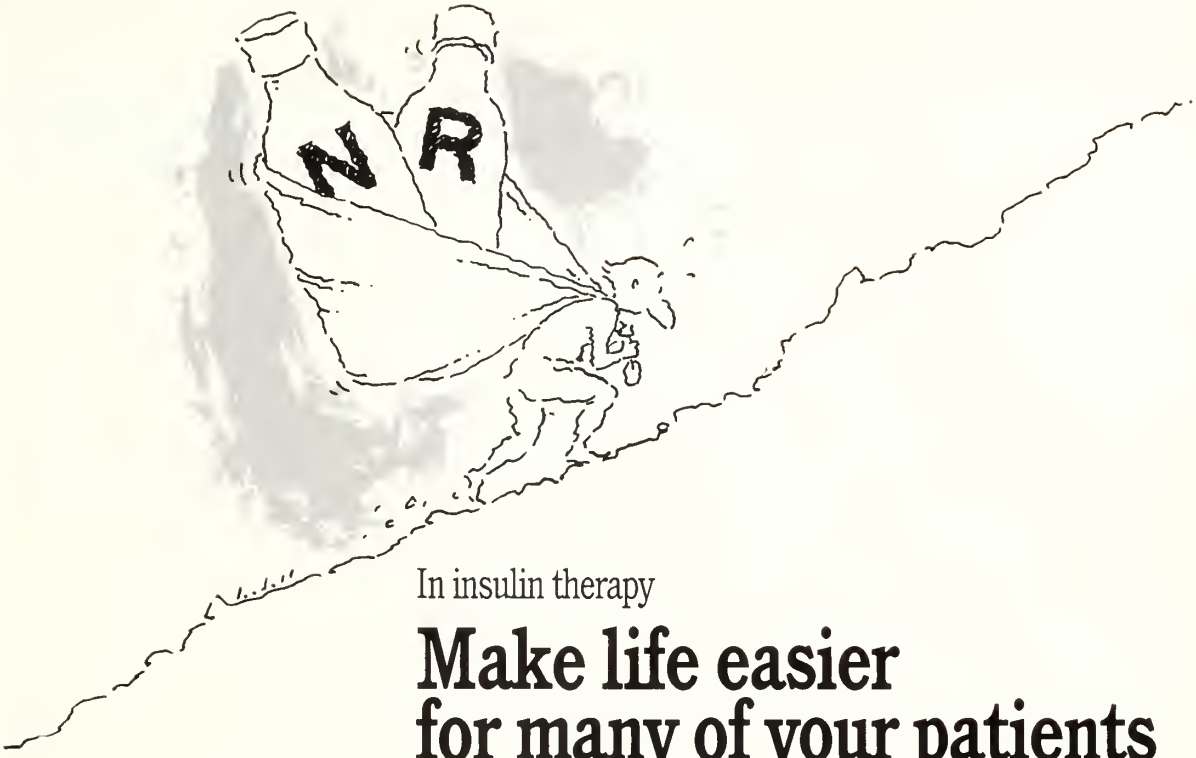
323 **Ethical Dilemmas in a Cross-cultural Context—A Chinese Example**
JESSICA H. MULLER, PhD, and BRIAN DESMOND, MD
From the Department of Family and Community Medicine, University of California, San Francisco, School of Medicine.

328 **Medical Disclosure and Refugees—Telling Bad News to Ethiopian Patients**
YEWOUBDAR BEYENE, PhD
From the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco.

333 **Older Russian Emigrés and Medical Care**
MERYL BROD, PhD, and SUZANNE HEURTIN-ROBERTS, PhD
From the Center for Clinical and Aging Services Research, San Francisco, California.

337 **Getting By at Home—Community-Based Long-term Care of Latino Elders**
STEVEN P. WALLACE, PhD, and CHIN-YIN LEW-TING, PhD
From the Department of Community Health Sciences, University of California, Los Angeles, School of Public Health.

(Continued on Page 228)



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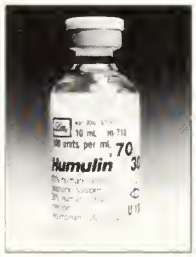

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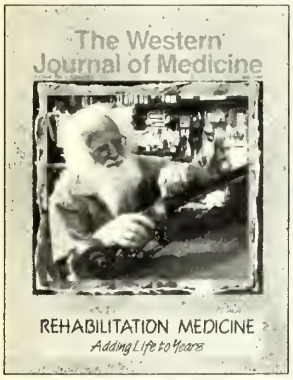

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- PHARMACOLOGIC APPROACHES TO THE TREATMENT OF COCAINE DEPENDENCE *Wanda A. Taylor and Mark S. Gold*

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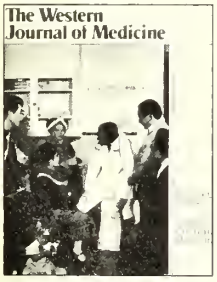

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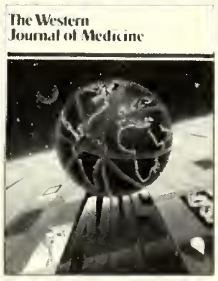

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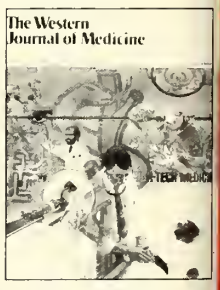

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(Continued from Page 224)

345 **The French Are Different—French and American Medicine in the Context of AIDS**

JAMIE FELDMAN, MA

From the Medical Scholar's Program, Department of Anthropology, University of Illinois, Urbana-Champaign, Urbana.

350 **The Business of Preventing African-American Infant Mortality**

JAN GATES-WILLIAMS, MA; M. NJERI JACKSON, PhD; VALATA JENKINS-MONROE, PhD; and LANDON R. WILLIAMS, MPP

From the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco; the Department of Political Science, Virginia Commonwealth University, Richmond; and the Department of Psychology, California School of Professional Psychology, Alameda, and the City Manager's Office, Berkeley, California.

357 **Health Policy and Ethnic Diversity in Older Americans—Dissonance or Harmony?**

LINDA A. WRAY

From the Ethel Percy Andrus Gerontology Center, Leonard Davis School of Gerontology, University of Southern California, Los Angeles.

362 **A Season in the Life of a Migrant Farm Worker in California**

JUAN VICENTE PALERM, PhD

From the Department of Anthropology, Center for Chicano Studies, University of California, Santa Barbara.

367 **Occupational Health Problems Among Migrant and Seasonal Farm Workers**

KETTY MOBED, MSPH; ELLEN B. GOLD, PhD; and MARC B. SCHENKER, MD, MPH

From the Division of Occupational/Environmental Medicine and Epidemiology, Department of Internal Medicine, University of California, Davis, and the Agricultural Health and Safety Center.

OTHER FEATURES

213 **Subscription Information**

234 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington**

378 **Classified Advertising**

390 **Western State Medical Associations' Meetings**

Poems: 300, 322, 344, 374

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BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported i placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg wit rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM S Capsules involving over 3000 patients, the most common events (ie, greate than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5% nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bund branch block, congestive heart failure, ECG abnormalities, hypotensio palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormalit hallucinations, insomnia, nervousness, paresthesia, personality chang somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mil elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepat warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritatio hyperglycemia, hyperuricemia, impotence, muscle cramps, nas congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliativ dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemi increased bleeding time, leukopenia, purpura, retinopathy, an thrombocytopenia. In addition, events such as myocardial infarction ha been observed which are not readily distinguishable from the natural histo of the disease in these patients. A number of well-documented cases generalized rash, characterized as leukocytoclastic vasculitis, have bee reported. However, a definitive cause and effect relationship between the events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 2 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsu of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

CARDIZEM® CD Product Information as of October 1991

CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Mattson R Prevey ML, et al. JAMA 1989;261(22):3973-3974

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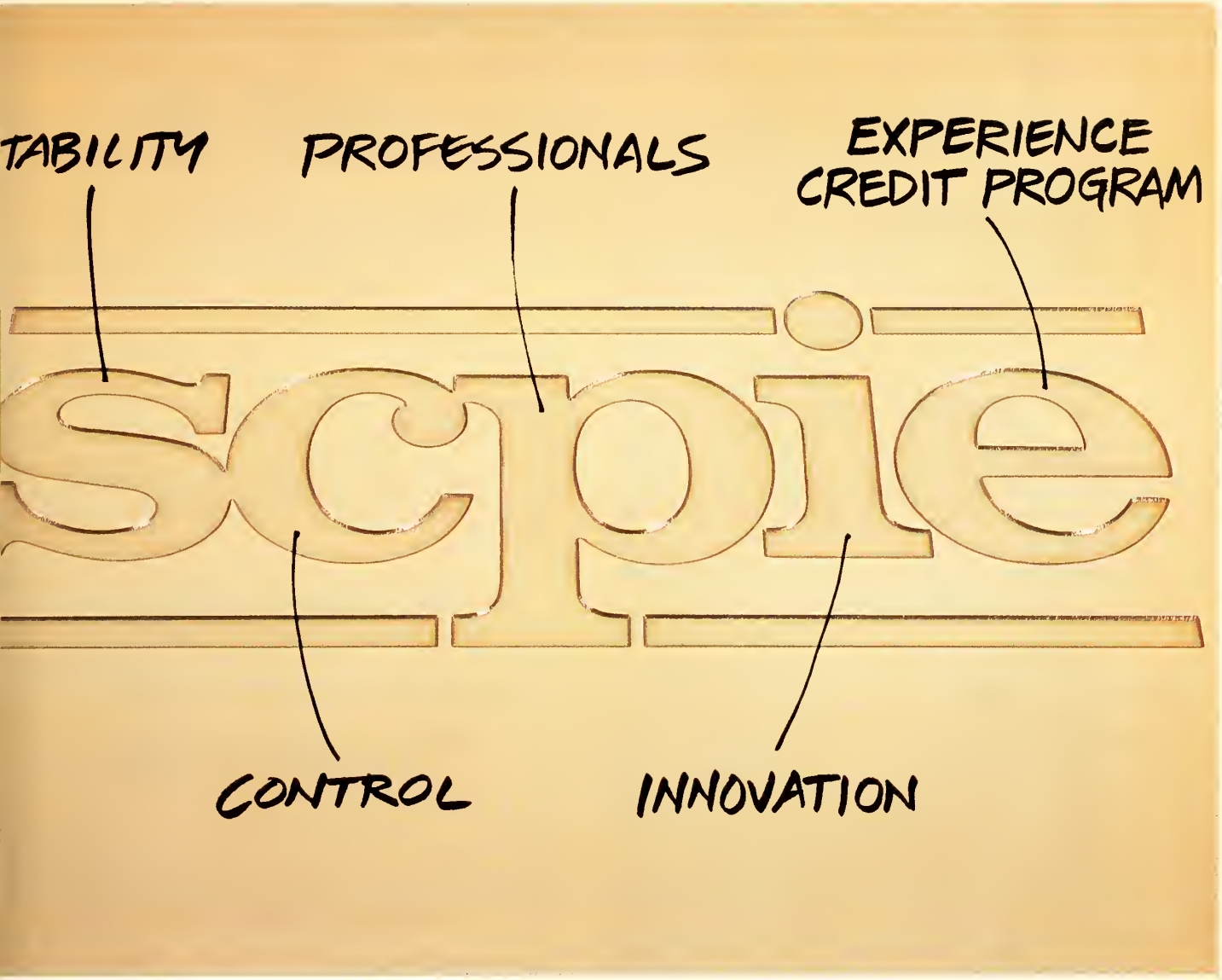

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

September 19—**Asthma Care for the Allergist of the Nineties.** Los Angeles Society of Allergy and Clinical Immunology at Westin South Coast Plaza Hotel, Costa Mesa. Sat. 8 hrs. Contact: Diann Smith, PO Box 84443, Los Angeles 90073. (310) 450-6092.

ANESTHESIOLOGY

October 22-25—**American Pain Society: 11th Annual Meeting.** American Pain Society at San Diego. Thurs-Sun. Contact: APS, 5700 Old Orchard Rd, Skokie, IL 60077-1057. (708) 966-5595.

October 25-31—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Resort, Poipu Beach, Kauai, Hawaii. Sun-Sat. 25 hrs. $395-$465. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 6-8—**Anesthesiology Update: 1992.** UCD at Monterey Plaza Hotel. Fri-Sun. 14 hrs. $350. Contact: UCD.

November 20-21—**Pain Management Conference.** UCD at Silverado Country Club. Fri-Sat. 12 hrs. $225. Contact: UCD.

January 6-9—**Anesthesia Update.** UCSD at Hotel del Coronado. Wed-Sat. Contact: UCSD.

January 29-31—**31st Clinical Conference in Pediatric Anesthesiology.** Children's Hospitals Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

CARDIOLOGY

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Medical Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

September 25-26—**Coronary Interventions: 1992.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sat. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 1-3—**Cardiology Update—1992.** American College of Cardiology at Quail Lodge, Carmel. Thurs-Sat. 12 hrs. $445. Contact: ACC, (800) 257-4739.

October 17—**Current Advancements in Interdisciplinary Management of Third Stage Stroke.** American Geriatrics Society at Stroke Activity Center, Palm Springs. Sat. 7 hrs. Contact: Diane Hanner, PO Box 355, Palm Springs 92263. (619) 323-7676.

January 21-23—**Cardiology '93.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, Conference Manager, PO Box 2586, La Jolla 92038. (619) 459-1564.

DERMATOLOGY

October 17-18—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

January 15-17—**Practical Dermatology & Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Wed-Fri. Contact: UCSD.

January 22-24—**Cutaneous Malignancies: 1993 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. $350. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

October 2-3—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Marina Del Rey. Fri-Sat. 15 hrs. Contact: Kathy Hester, (800) 451-7475.

October 10—**Emergency Medicine.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

October 19-23—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 26-30—**21st Annual Topics in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 32 hrs. $560. Contact: UCSF.

October 28-November 1—**Wound Management Workshop.** UCSD at San Diego Hilton Beach & Tennis Resort. Wed-Sun. Contact: UCSD.

October 29-November 1—**14th Year Biannual Wound Management Workshop.** UCSD at La Jolla Marriott. Thurs-Sun. 18 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 5-6—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Thurs-Fri. 15 hrs. $295-$495. Contact: Kathy Hester, (800) 451-7475.

November 9-13—**Emergency Medicine Symposia III.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

December 6-11—**Current Concepts in Emergency Care: 13th Annual Conference.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Jeannine Whidbee, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

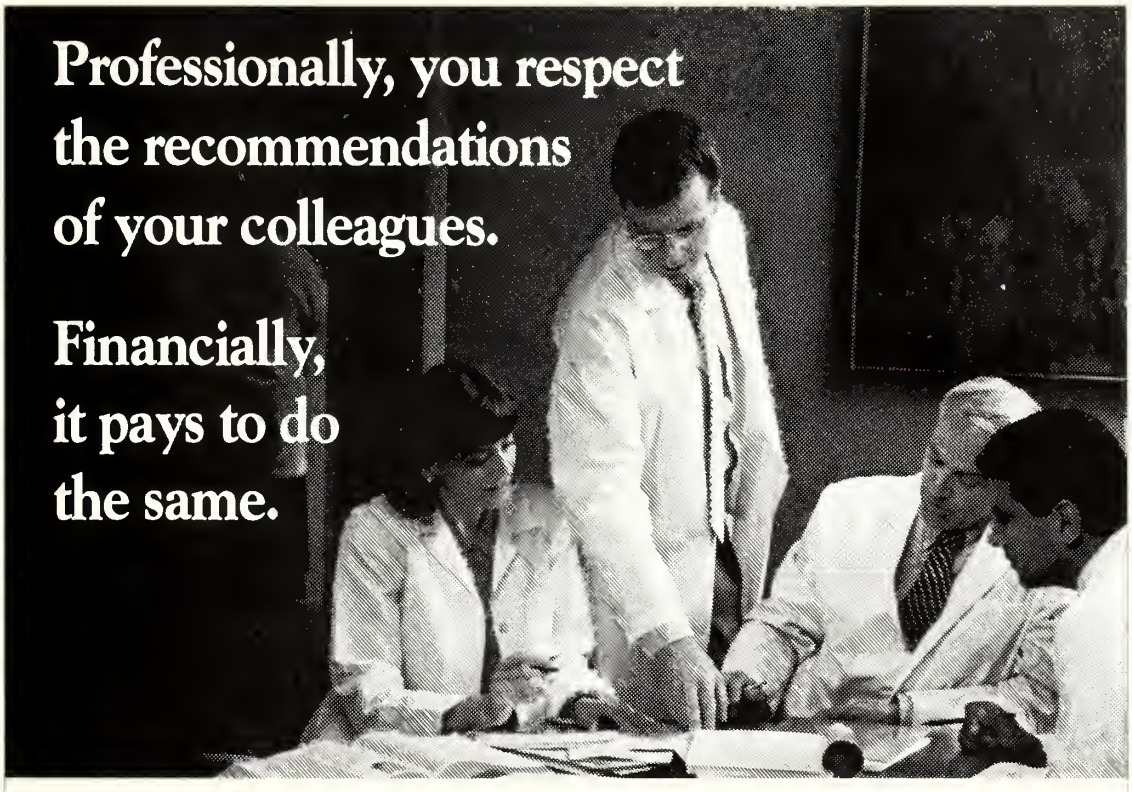
UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 236)



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Beverly Hills:	310-550-3333	*Downtown* San Diego:	619-525-1540	in Carmel:	408-624-9597	in Sonoma:	707-996-1344
Torrance:	310-542-6767	La Jolla:	619-597-2700	Palo Alto:	415-329-8300	Walnut Creek	510-947-1311
Downtown Los Angeles:	213-689-4542	Indian Wells:	619-341-7017	Burlingame	415-347-9595	in Oakland	510-339-6768
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CONTINUING MEDICAL EDUCATION

(Continued from Page 234)

December 7-11—**Emergency Medicine Symposia II.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

January 13-17—**The California Trauma Conference.** UCSD at Hotel del Coronado. Mon-Fri. 20 hrs. $400. Contact: UCSD.

January 18-22—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

January 23-30—**Wound Management.** UCSD at Royal Waikoloan, Kohala Coast, Island of Hawaii. 1 week. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-27—**Update: Controversies in Emergency & Primary Care.** American Institute of Postgraduate Education at Royal Lahaina Resort, Maui, Hawaii. 1 week. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

ENDOCRINOLOGY/METABOLISM

November 10-14—**VIIth International Symposium on the Biology of Vascular Cells.** Scripps Clinic and Research Foundation at Princess Resort Mission Bay, San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 19-20—**New Horizons in Diabetes Therapy.** Scripps Clinic and Research Foundation at Scripps Memorial Hospital, La Jolla. Fri-Sat. $175. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

FAMILY PRACTICE/PRIMARY CARE

September 23-25—**7th Annual Primary Care Medicine: Principles and Practice.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $485. Contact: UCSF.

September 25—**Primary Care Issues in Cardiovascular Disease.** Alta Bates Medical Center at Center Auditorium. Fri. 7 hrs. $75. Contact: Mary Grim, (510) 204-1420.

October 15-18—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Maui Inter-Continental Hotel, Hawaii. Thurs-Sun. 16 hrs. $281-$375. Contact: UCLA Extension.

October 26-29—**Primary Care Update.** Interstate Postgraduate Medical Association of North America at Riviera Hotel & Casino, Las Vegas. Mon-Thurs. 24 hrs. $225-$325. Contact: IPMA, PO Box 5474, Madison, WI 53705. (608) 257-1401.

November 12-15—**CME/GOLF Meeting.** Nevada Academy of Family Physicians at Rio Hotel, Las Vegas. Thurs-Sun. 17 hrs. $225. Contact: Shone Ariotti, 895 Adams Blvd, Boulder City, NV 89005. (702) 293-0406.

February 12-14—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

September 26—**Selected Topics in Geriatric Medicine.** UCLA at Miramar Sheraton Hotel, Santa Monica. Sat. 6 hrs. $40. Contact: UCLA Extension.

November 16-18—**Geriatrics Update—1992.** Sharp Memorial Hospital at Loew's Coronado Bay Resort. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

HEMATOLOGY

November 14—**Hyperlipidemia Update: 1992.** UCD at Cancer Center Auditorium, Sacramento. Sun. Contact: UCD.

December 4—**Current Issues in Hemophilia Care.** Orthopaedic Hospital Los Angeles at Hyatt Regency Alicante, Anaheim. Sat. 6 hrs. $100. Contact: Hemophilia Care, Meeting Management, 5665 Oberlin Dr, #110, San Diego 92121. (619) 453-6222.

February 14-17—**Clinical Hematology and Oncology: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sun-Wed. 18 hrs. $385. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

INFECTIOUS DISEASES

September 19—**AIDS.** Sutter Health at Sacramento Inn. Sat. Contact: Sutter Health, (916) 733-3883.

October 21—**22nd Annual Respiratory/Infectious Diseases Symposium.** Enloe Hospital at Esplanade Building, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

November 13-15—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

December 14-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

February 4-6—**11th Annual Practical Update of Infectious Diseases.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. 12 hrs. $160. Contact: UCD.

INTERNAL MEDICINE

September 17-19—**American Gastroenterological Association 1992 Fall Postgraduate Course.** AGA at Westin St. Francis, San Francisco. Thurs-Sat. Contact: SLACK Inc, 6900 Grove Rd, Thorofare, NJ 08086-9447. (609) 848-1000.

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Sat-Mon. Contact: UCSD.

February 5-7—**State of the Art Urology.** UCLA at Ritz-Carlton, Marina del Rey. Fri-Sun. Contact: UCLA Extension.

NEUROLOGY

October 9-11—**Neurology for the Non-Neurologist.** Medical Education Resources at Parc Fifty-Five, San Francisco. Fri-Sun. Contact: MER, 1500 W Canal, Ste 500, Littleton, CO 80120-4528. (303) 798-5731.

October 23-24—**Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery and Anesthesiology.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. Contact: UCLA Division of Neurosurgery, (310) 206-0626.

February 4-6—**16th Annual: Neurology for Non-Neurologists.** UCSD at Doubletree Hotel Horton Plaza, San Deigo. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 11-13—**26th Annual Recent Advances in Neurology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. Contact: UCSF.

OB/GYN

September 23-25—**Contemporary Obstetrical & Transvaginal Ultrasound.** UCSD. Wed-Fri. Contact: UCSD.

October 2-3—**Operative Laparoscopy.** UCLA at Loews Santa Monica Beach Hotel. Fri-Sat. 15 hrs. $500-$700. Contact: UCLA Extension.

October 3-4—**Ultrasound Update: 1992.** UCD at Sacramento. Sat-Sun. Contact: UCD.

October 24—**Women's Health and Breast Cancer.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. Contact: UCD.

December 3-5—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas. Thurs-Sat. $250. Contact: Brenda Ram, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

February 11-14—**48th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: C. James Dowden, OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

OCCUPATIONAL/ENVIRONMENTAL

October 15-18—**36th Annual Western Occupational Health Conference.** American College of Occupational and Environmental Medicine at Sheraton Harbor Island, San Diego. Thurs-Sun. 18 hrs. $250-$335. Contact: WOHC, 50 First St, Ste 300, San Francisco 94105-2411. (415) 764-4803.

October 19-30—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. 1½ wks. 80 hrs. $1,400. Contact: UCSF.

November 2-6—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

January 25-February 5—**Occupational & Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. 1½ weeks. 80 hrs. $1400. Contact: UCSF.

ONCOLOGY

October 12-18—**18th Annual Lukes Lymphoma Conference.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Sun. 25 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

(Continued on Page 241)

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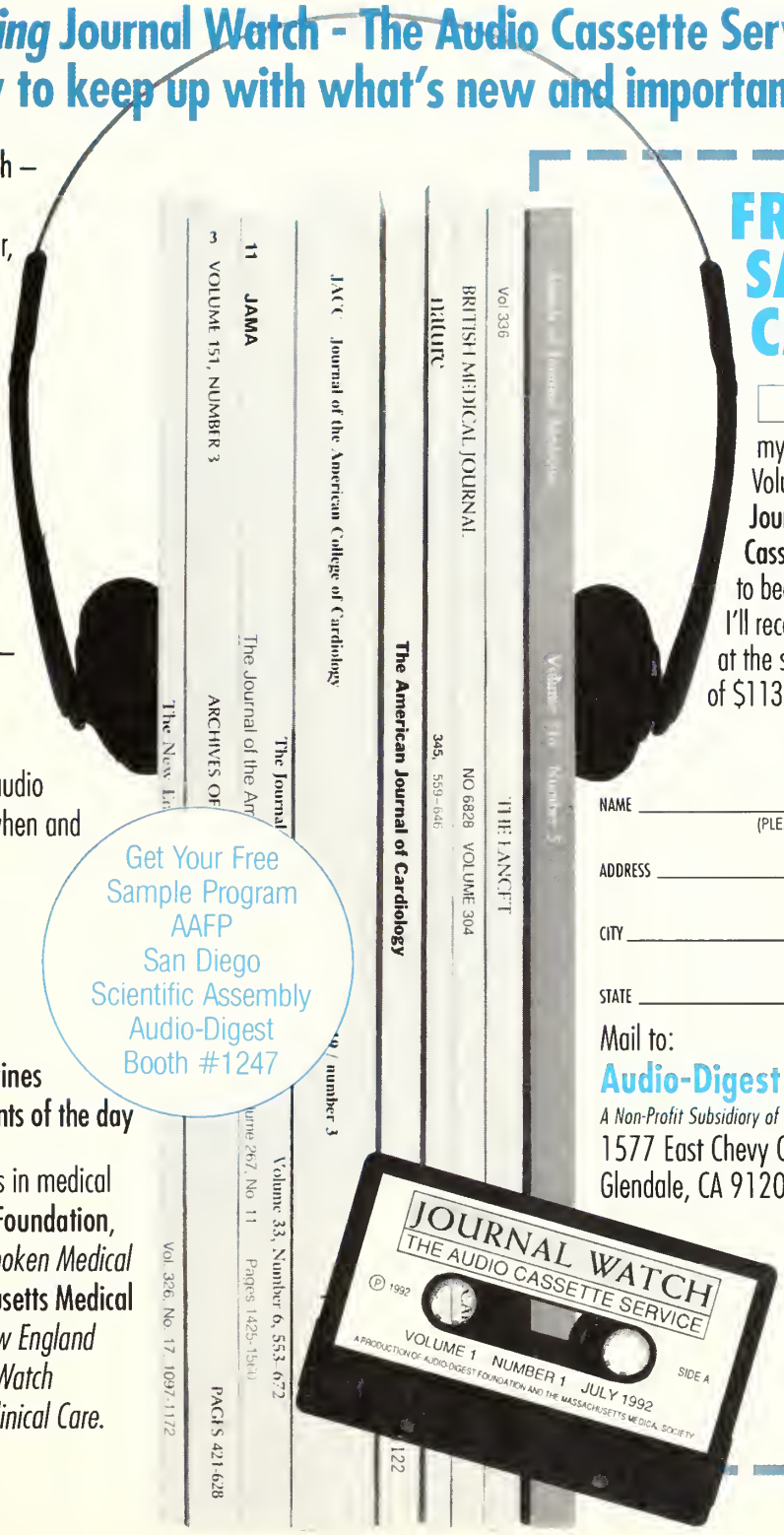

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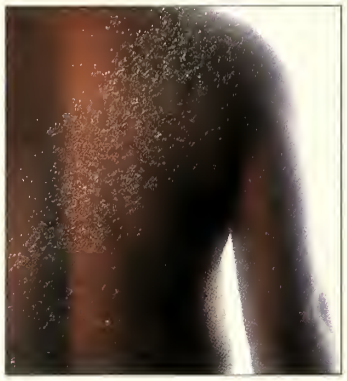
Because coexisting conditions often complicate hypertension...

DynaCirc® (isradipine) puts their safety first.



Facilitates renal function.

- No clinically significant change in serum creatinine[1,2] or creatinine clearance[1,3]
- No clinically significant effect on glomerular filtration rate[3-6]
- Maintains or decreases filtration fraction[1,3,6]

Maintains cardiac performance.

- No significant effect on heart rate*[7-10]
- No adverse effect on cardiac conduction[11,12] or contractility†[3,10,13-15]
- No alteration of digoxin clearance[16]

Does not compromise metabolic parameters.

- No clinically significant effect on serum glucose metabolism[17]
- No effect on glucose tolerance, insulin secretion or insulin action in NIDDM patients[17]
- No clinically significant effect on lipid metabolism[18,19]

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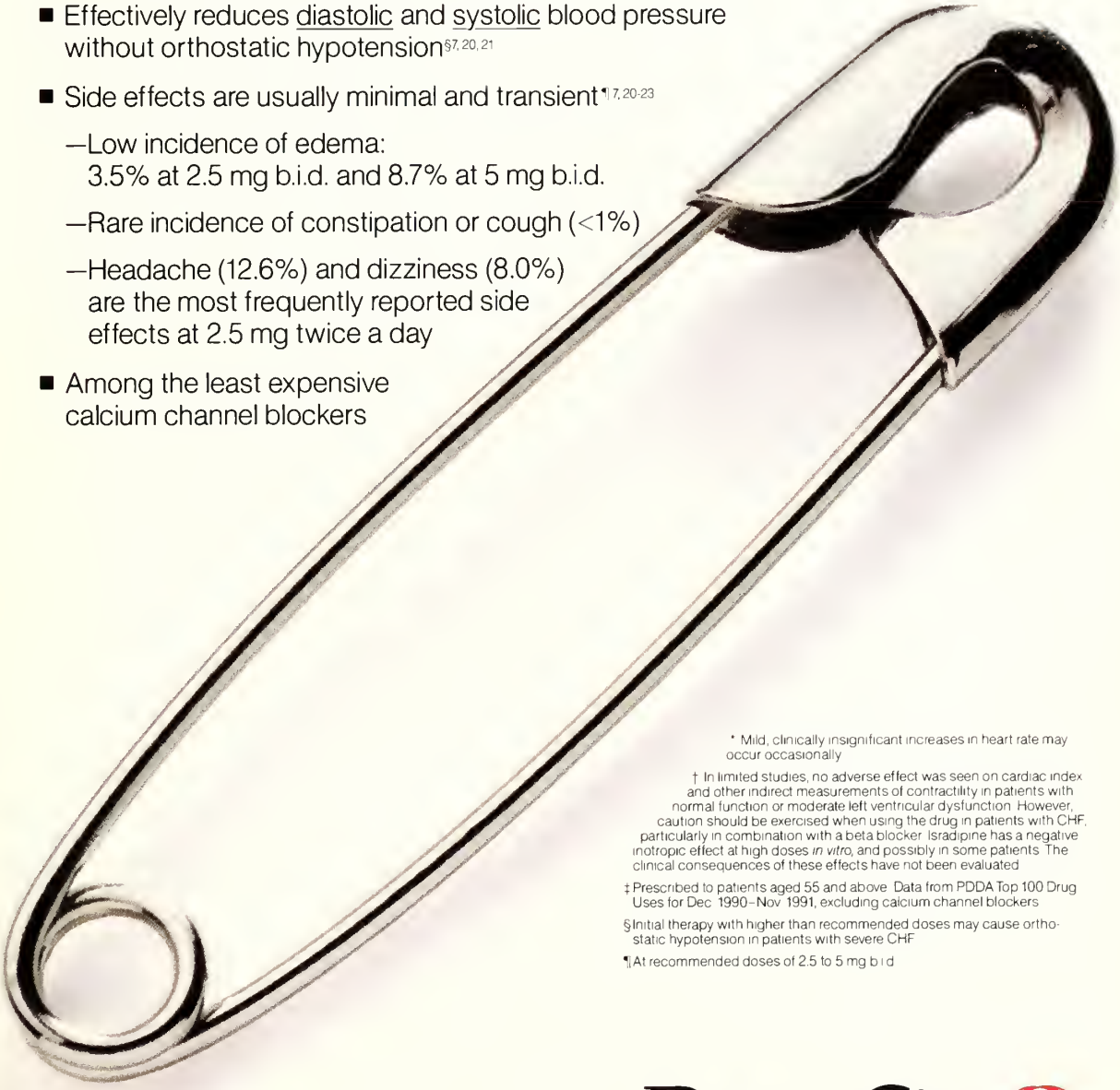
- No known contraindications except for hypersensitivity to DynaCirc
- No significant interactions with the 20 most-commonly prescribed drugs‡
- Effectively reduces diastolic and systolic blood pressure without orthostatic hypotension§[7,20,21]
- Side effects are usually minimal and transient¶[1,7,20-23]
  - —Low incidence of edema: 3.5% at 2.5 mg b.i.d. and 8.7% at 5 mg b.i.d.
  - —Rare incidence of constipation or cough (<1%)
  - —Headache (12.6%) and dizziness (8.0%) are the most frequently reported side effects at 2.5 mg twice a day
- Among the least expensive calcium channel blockers



* Mild, clinically insignificant increases in heart rate may occur occasionally

† In limited studies, no adverse effect was seen on cardiac index and other indirect measurements of contractility in patients with normal function or moderate left ventricular dysfunction. However, caution should be exercised when using the drug in patients with CHF, particularly in combination with a beta blocker. Isradipine has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. The clinical consequences of these effects have not been evaluated.

‡ Prescribed to patients aged 55 and above. Data from PDDA Top 100 Drug Uses for Dec. 1990–Nov. 1991, excluding calcium channel blockers.

§ Initial therapy with higher than recommended doses may cause orthostatic hypotension in patients with severe CHF.

¶ At recommended doses of 2.5 to 5 mg b.i.d.

DynaCirc®

2.5 mg capsules (isradipine) 5 mg capsules

For Safety's Sake™

Please see following page for brief summary of full Prescribing Information.

BRIEF SUMMARY
Please see package insert for full prescribing information.

DYNACIRC® (isradipine) CAPSULES

INDICATION

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None

PRECAUTIONS

General: *Blood Pressure*: Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses. *Use in Patients with Congestive Heart Failure*: Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker. **Drug Interactions**: *Nitroglycerin*: DynaCirc® has been safely coadministered with nitroglycerin. *Hydrochlorothiazide*: A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect. *Propranolol*: In a single dose study in normal volunteers coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol. *Digoxin*: The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, non-renal and total body clearance of digoxin. *Fentanyl Anesthesia*: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. A comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats. **Pregnancy**: *Pregnancy Category C*: There are no adequate and well controlled studies in pregnant women. DynaCirc® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers**: It is not known whether DynaCirc® is excreted in human milk. A decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**: Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience. Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia), and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions (vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations, and gastrointestinal disturbances. The following adverse reactions have been reported by 1% or greater of patients receiving DynaCirc® at any dose (N=934): headache (13.7%), dizziness (7.3%), edema (7.2%), palpitations (4.0%), fatigue (3.9%), flushing (2.6%), chest pain (2.4%), nausea (1.8%), dyspnea (1.8%), abdominal discomfort (1.7%), tachycardia (1.5%), rash (1.5%), pollakiuria (1.5%), weakness (1.2%), vomiting (1.1%), diarrhea (1.1%). The following adverse events were reported in 0.5-1% of the isradipine-treated patients in hypertension studies, or are rare, but more serious events from this and other data sources, including postmarketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain. **Skin**: pruritus, *urticaria*. **Musculoskeletal**: cramps of legs/feet. **Respiratory**: cough. **Cardiovascular**: shortness of breath, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure*. **Gastrointestinal**: abdominal discomfort, constipation, diarrhea. **Urogenital**: nocturia. **Nervous System**: drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, *syncope, paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke*. **Autonomic**: hyperhidrosis, visual disturbance, dry mouth, numbness. **Miscellaneous**: throat discomfort, *leukopenia, elevated liver function tests*.

[DECEMBER 31, 1990 DYN-Z2]

References

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(Continued from Page 236)

October 24—**Melanoma and Pigmented Lesions.** Stanford University Medical Center at Fairchild Auditorium, Stanford. Sat. Contact: STAN.

October 26-28—**16th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, Cancer Symposium, 5665 Oberlin Dr, #110, San Diego 92121. (619) 453-6222.

November 5-8—**Prostate Cancer.** Sutter Health at Hyatt Regency, Sacramento. Thurs-Sun. Contact: Sutter Health, (916) 733-3883.

OPHTHALMOLOGY

October 10—**The Diabetic Eye.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6 hrs. $50. Contact: UCD.

December 10-12—**Ophthalmic Surgical Complications: OOPS—What Do I Do Now?** UCSF at Ritz-Carlton Hotel and UCSF Campus, San Francisco. Thurs-Sat. 12 hrs. $200-$375. Contact: UCSF.

ORTHOPEDICS

October 31—**Orthopedics Symposium.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

November 5-6—**Low Back Pain and Its Relation to the Sacroiliac Joint.** UCSD at San Diego Convention Center. Thurs-Fri. 12 hrs. $335. Contact: UCSD.

November 19-21—**San Diego Spine Symposium.** UCSD at San Diego Marriott. Thurs-Sat. 11 hrs. Contact: UCSD.

December 3—**9th Annual Symposium on Common Musculoskeletal Problems: Current Concepts in Diagnosis and Management of Arthritis.** VA Medical Center Sepulveda. Thurs. 6 hrs. Contact: Arun Mehta, MD, VA Med Ctr, RMS 117, Sepulveda 91343-2036. (818) 895-9344.

December 9-13—**Fall Symposium on Back Pain.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

OTOLARYNGOLOGY

September-December 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Mon-Sat. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

November 5-7—**Otolaryngology Update: 1992.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $395. Contact: UCSF.

PATHOLOGY

October 10—**Fine Needle Aspiration: Advanced Tutorial XXI.** UCSF. Sat. 12 hrs. $650. Contact: UCSF.

October 17—**32nd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Irvine Marriott. Sat. Contact: Sylvie Tarro, (310) 641-8152.

October 26-30—**Urological Pathology: Current Concepts and Recent Developments.** American Society of Clinical Pathologists at Santa Barbara. Mon-Fri. 25.5 hrs. $690. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (312) 738-1336.

PEDIATRICS

September 21-26 & October 19-24—**Lactation Management Education Program.** UCSD at Wellstart, San Diego. Mon-Sat. Contact: UCSD.

October 19-22—**17th Annual Pediatrics for the Practitioner.** Long Beach Memorial at Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact: Eunice Larson, MD, (310) 595-3422.

October 22-26—**Lactation Educator Training Program.** UCLA at St Agnes Medical Center, Fresno. Thurs-Mon. 22.5 hrs. $740. Contact: UCLA Extension.

January 26-30—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Hyatt Regency, La Jolla. Tues-Sat. Contact: Center for Child Protection, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4950.

February 15-17—**Pediatrics Update.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

February 26-28—**Current Concepts in Pediatric Medicine: 1993.** Children's Hospital San Diego and American Academy of Pediatrics at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Continuing Education, 8001 Frost St, San Diego 92123. (619) 576-4072.

PSYCHIATRY

November 5-7—**Addiction Medicine: 1992 Review Course and Workshops.** California Society of Addiction Medicine and American Society of Addiction Medicine at Ramada Renaissance Hotel, Long Beach. Thurs-Sat. 20 hrs. $350. Contact: CSAM, 3803 Broadway, Oakland 94611. (510) 428-9091.

November 13-15—**38th Annual Group Therapy Symposium.** UCSF at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. Contact: UCSF.

February 27—**Sleep Apnea: New Insights into Pathophysiology and Treatment.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PULMONARY MEDICINE

September 17-19—**11th Annual Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 15 hrs. $410. Contact: UCSF.

September 18-19—**Controversies and Advances in Pulmonary Care.** California Thoracic Society at Hotel Nikko, San Francisco. Fri-Sat. 10 hrs. Contact: CTS, 202 Fashion Ln, #219, Tustin 92680. (714) 730-1944.

RADIOLOGY

September 20-23—**UCLA Digital Radiography and Image Management Networking Conference.** UCLA Medical Center at Miramar Sheraton Hotel, Santa Monica. Sun-Wed. 16 hrs. $345. Contact: UCLA.

September 21-23—**Digital Radiography and Image Management Networking.** UCLA Radiological Sciences at Miramar Sheraton Hotel, Santa Monica. Mon-Wed. 16 hrs. $345. Contact: UCLA Radiological Sciences, (310) 206-7435.

October 1-4—**Western Neuroradiological Society Annual Meeting.** Western Neuroradiological Society at Ritz-Carlton, San Francisco. Thurs-Sun. 11.5 hrs. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 3-4—**Ultrasound Update: 1992.** UCD at Red Lion Inn, Sacramento. Sat-Sun. 10 hrs. $180-$225. Contact: UCD.

October 24-25—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-30—**17th Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25.25 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 29-November 1—**Current Concepts of Magnetic Resonance.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 19.5 hrs. $450-$550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 30-November 1—**12th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 2-6—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Mon-Fri. 15 hrs. $400. Contact: UCSD.

November 13-15—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 28-January 2—**Year End Review of Imaging and Intervention.** UCSD at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Sat. 25 hrs. $550-$595. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 16-17—**Interventional Radiology Update.** Stanford University at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 7.5 hrs. $200-$250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 18-20—**Neuroradiology Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 17.5 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 21-24—**Breast Imaging Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 17.25 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

(Continued on Page 242)

(Continued from Page 241)

February 15-19—**Diagnostic Imaging Update: Mammography, MRI, Body Imaging, Neuroradiology, Pediatrics.** Stanford University Medical Center at Ritz-Carlton, Palm Beach. Mon-Fri. 23.75 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 22-26—**Diagnostic Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Kapalua Bay, Maui, Hawaii. Mon-Fri. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

October 16-18—**Hip and Knee Reconstructive Surgery: 1992.** UCLA at Westin Hills Resort, Rancho Mirage. Fri-Sun. 14 hrs. $595. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. Sun-Sat. 36 hrs. $500-$995. Contact: UCLA Extension.

January 24-29—**16th Annual Postgraduate Assembly in Surgery.** UCSD at Doubletree Hotel, Horton Plaza, San Diego. Sun-Fri. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

September 24-27—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. Thurs-Sun. Contact: UCLA Extension.

September 30-October 3—**39th Annual Meeting of the Medical Society of the United States and Mexico at Napa Valley.** Wed-Sat. Contact: Beverly Richter, (602) 246-8901.

December 24-29—**Advances in Medicine '92.** Hawaii Medical Association at Kaanapali Beach, Maui, Hawaii. Fri-Wed. 16 hrs. $450. Contact: Joe Harrison, MD, PO Box 833, Makawao, HI 96768. (808) 878-7657.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

September 16-17—**Neonatal Resuscitation Hospital-Based Instructor Course.** Children's Hospital, Denver. Wed-Thurs. Contact: Pat Winter, (303) 861-6668.

September 17, 24, October 1, 8—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Four consecutive Thursdays. Contact: Trish Beachy, (303) 270-8376.

September 18-23—**Primary Care Computing.** University of Colorado's CME in the Rockies at the Given Institute, Aspen. Fri-Wed. Contact: U of Colo.

September 20-25—**Wilderness Medical Society—8th Annual Scientific Meeting.** Keystone. Sun-Fri. Contact: Wilderness Medical Society, PO Box 2463, Indianapolis, IN 46206. (317) 631-1745.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

September 25-26—**Montrose Memorial Hospital Fall Clinics.** Montrose Pavilion, Montrose. Fri-Sat. Contact: N. Robert Brethouwer, DO, (303) 249-2211.

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 9-13—**38th Annual Family Practice Review.** University of Colorado Health Sciences Center, Denver. Wed-Sun. Contact: U of Colo.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

January 22-24—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs Medical Center at Beaver Run Resort and Conference Center, Breckenridge. Fri-Sun. Contact: Victoria Hall or Karen Babcock, (303) 393-2826, or FAX (303) 393-4656.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 18-19—**New Mexico Chapter, American College of Surgeons, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Fri-Sat. Contact: William Abbott, MD, 711 Encino Pl NE, Albuquerque 87102. (505) 843-7901; or Bonnie Smith at the New Mexico Medical Society, (505) 828-0237 or (800) 748-1596.

September 26-27—**Pediatric Infectious Diseases for the '90s.** Plaza Hotel, Las Vegas. Sat-Sun. Contact: Marilyn Stark, New Mexico Chapter, American Academy of Pediatrics, 7605 Mountain Rd NE, Albuquerque 87110. (505) 265-7431; or George Bunch, MD, 501 7th St, Las Vegas 87701. (505) 425-3566.

October 8-11—**The American Academy of Pain Management 1992 Annual Conference.** Hyatt Regency Hotel, Albuquerque. Thurs-Sun. Contact: Janice Mohr, American Academy of Pain Management, 3600 Sisk Rd, Ste 2-D, Modesto, CA 95356. (209) 545-0754.

October 9-10—**Effective Psychotherapy: Research and Practice.** Sheraton Old Town Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

October 22-24—**Practical Orthopaedics in the Primary Care Setting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 22-24—**Infectious Disease: Issues and Challenges in Obstetrics and Gynecology.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 30-November 1—**The Emotional Life of the Infant: Clinical Applications.** Hilton Hotel, Albuquerque. Fri-Sun. Contact: UNM SOM.

November 6-7—**Update for Radiographers.** Four Seasons Quality Inn, Albuquerque. Fri-Sat. Contact: UNM SOM.

December 3-5—**American College of Physicians, New Mexico Chapter, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

December 11-12—**Trauma Update 1992.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

(Continued on Page 244)

AMERICAN MEDICAL WOMEN'S ASSOCIATION

77TH ANNUAL MEETING

NOVEMBER 11-15, 1992

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(Continued from Page 242)

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 16-19—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS: Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV: Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 16—**Soft Tissue Excision & Repair for the Non-Plastic Surgeon.** Seattle. Wed. Contact: Northwest Hospital, (206) 368-1623.
September 21-22—**HIV/AIDS Clinical Update.** Seattle. Mon-Tues. Contact: NW AIDS Education and Training Center, (206) 720-4252.
September 21-22—**Adult Critical Care.** Tacoma. Tues-Wed. Contact: Multicare, (206) 592-1221.
September 23-24—**The Birth of Bioethics.** Seattle. Wed-Thurs. Contact: U/W.
September 23-24—**Critical Care.** Tacoma. Thurs-Fri. Contact: Multicare, (206) 594-1221.
September 24—**OB Issues.** Everett. Fri. Contact: PNMEI, (206) 258-6322.
September 24-26—**Rural Health Care Financing Conference.** Seattle. Fri-Sun. Contact: U/W School of Medicine, (206) 543-9952.
October 1-4—**Washington State Medical Association Annual Meeting.** Yakima. Thurs-Sun. Contact: WSMA.
October 2—**Infectious Diseases Update.** Seattle. Fri. Contact: U/W.
October 3-4—**ACLS Course.** Seattle. Sat-Sun. Contact: Highline Community Hospital, (206) 431-5324.
October 8—**Family Practice Update.** Seattle. Fri. Contact: Providence Hospital, (206) 320-2552.
October 8-9—**Common Office Problems.** Tacoma. Fri-Sat. Contact: College of Medical Education, (206) 627-7137.
October 14—**Indoor Air Quality.** Seattle. Wed. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.
October 20-23—**Development and Application of Biomarkers to the Study of Human Health Ethics.** Seattle. Tues-Fri. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.
October 22—**Pain Management.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.
October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.
October 23—**NPCCare Consortium.** Seattle. Fri. Contact: Children's Hospital, (206) 526-2501.
October 30—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.
October 30—**Preventative Health Care in the Elderly.** Seattle. Fri. Contact: Northwest Hospital, (206) 368-1623.
October 30-31—**Primary Care for Women.** Seattle. Fri-Sat. Contact: VMMC.
October 30-31—**Black Culture Health.** Seattle. Fri-Sat. Contact: Providence Hospital, (206) 320-2552.
October 31-November 1—**PALS Instructor Course.** Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.
November 6—**Infectious Disease Update.** Tacoma. Fri. Contact: PCMS CME.
November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.
November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.
November 14-15—**Travel Medicine Update.** Seattle. Sat-Sun. Contact: U/W.
November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.
November 20—**GI Day.** Seattle. Fri. Contact: PCMS CME.
November 21—**Arthrocentesis & Injection Techniques.** Seattle. Sat. Contact: U/W.
December 4—**Rehabilitation Issues in Aging.** Seattle. Fri. Contact: U/W.
December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.
December 10-11—**ACLS Course.** Tacoma. Thurs. Contact: PCMS CME.
December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.
December 10-12—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.
December 15-16—**Introduction to Industrial Hygiene.** Seattle. Tues-Wed. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.

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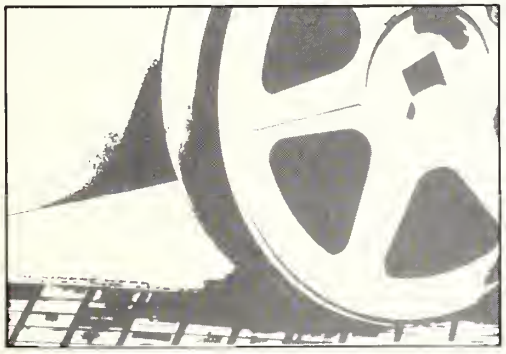

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References: 1. Data on file, Bristol-Myers Squibb Company **2.** Cohn JB, Bowden CL, Fisher JG, Rodos JJ. Double-blind comparison of buspirone and clorazepate in anxious outpatients with or without depressive symptoms. *Psychopathology* 1992;25:10-21 **3.** Feighner JP, Cohn JB. Analysis of individual symptoms in generalized anxiety—a pooled, multistudy, double-blind evaluation of buspirone. *Neuropsychobiology* 1989;21:124-130 **4.** Lader M. Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26 **5.** Newton RE, Marunycz JD, Alderdice MT, Napoliello MJ. Review of the side-effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General*** – *Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients – Patients should be instructed to inform their physician about any medications, prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions – Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations of SGPT (ALT) in a few patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol concentrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone was given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

Carcinogenesis, Mutagenesis, Impairment of Fertility – No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects – Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers – Administration to nursing women should be avoided if clinically possible.

Pediatric Use – The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly – No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function – Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed*** – The more commonly observed untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment – The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials – Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation – The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular* – frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System* – frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT* – frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine* – rare: galactorrhea, thyroid abnormality. *Gastrointestinal* – infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary* – infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal* – infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological* – infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory* – infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function* – infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin* – infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory* – infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous* – infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience – Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: ***Controlled Substance Class*** – Not a controlled substance.

Physical and Psychological Dependence – Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms*** – At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdosage Treatment – General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

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Cross-cultural Medicine
A Decade Later

Beyond Words

A word is dead
When it is said,
some say.

I say it just
Begins to live
That day.

EMILY DICKINSON

"CROSS-CULTURAL MEDICINE—A DECADE LATER" is about words, about understanding the meaning of words. This special issue of the journal acknowledges the liveliness of words and also the possibility that they can be misinterpreted. Therefore, it is also about language, language that goes beyond words. It describes, for example, body language—gestures, stances, glances. It illustrates why words and behaviors may have diverse meanings in diverse settings. This issue cites experiences, beliefs, and fears of people who, although patients, may be strangers. It vividly profiles individuals and then discusses the groups they represent.

"Cross-cultural Medicine—A Decade Later" was carefully and wisely shepherded by Judith C. Barker, PhD, medical anthropologist at the University of California, San Francisco, with the collaboration of Margaret M. Clark, PhD, editor of the 1983 volume. Papers have been written by experts who provide data whenever they are available. Although the paucity of data in many areas has led some authors to make hypotheses rather than assertions, they have tried to avoid generalizations and stereotypes.

The Kaiser Family Foundation, noting the special issue's distinguished forebear, provided substantial funds to assure broad distribution of this new volume. This issue will inform professionals and policymakers in public and private venues across the country and around the world about the complexities of assuring appropriate health care when traditions differ. It will also provide practical approaches to cultural conflicts.

"Cross-cultural Medicine—A Decade Later" is testimony to the courage of many who have suffered greatly and who need to be understood and to receive care that recognizes their backgrounds. It is also testimony to the acumen and devotion of scientists who work with and do research with underserved minorities. This special issue of the journal is meant to answer questions and propose solutions, to satisfy curiosity, to prick consciences and expand consciousness.

As the world becomes more intertwined and as we depend more upon each other, our communication must improve as fast as the forces that bring us together. Smooth and open communication is fundamental to healing and to building communities. Therapeutic relationships and respect grow as the strange becomes familiar and differences become valued. We hope the words of this special issue will live far beyond the days they were written. We think that "Cross-cultural Medicine—A Decade Later" will broaden perspectives, brighten lives, and lead to sound, responsive public policy and health care.

LINDA HAWES CLEVER, MD

Cross-cultural Medicine
A Decade Later

Cultural Diversity—Changing The Context of Medical Practice

JUDITH C. BARKER, PhD, *Special Editor*

(Barker JC: Cultural diversity—Changing the context of medical practice, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:248-254)

Since 1983 when the first WESTERN JOURNAL OF MEDICINE issue on cross-cultural medicine was published,[1] interest in biomedicine has grown. The various social sciences of medicine—medical anthropology; medical sociology; health psychology; health economics; medical geography; and health policy, planning, and administration—are no longer relatively new and easily dismissed ventures. Programs in medical social science have been started in social science departments and health professional schools. Medical anthropologists teach, conduct research, examine policies, or plan or administer private or government-funded programs, both within the United States and abroad.

Organized interest groups in medical anthropology abound. In these groups, membership tends to be growing in number, multidisciplinary in orientation, and vigorous in the sponsorship of symposia or publications. Since 1983 several established sociomedical journals have not merely survived but have grown in importance and stature. New journals have arisen to expand examination of the relationship between health and population diversity. Collected works have appeared that examine the relationship of anthropology to epidemiology,[2] the nature of biomedicine itself,[3,4] and theoretic and methodologic issues.[5] A handful of now-classic works exist about specific subcultural or immigrant populations in the United States.[6-8] Books dealing with various aspects of cross-cultural clinical practice and aimed specifically at practitioners, primarily at nurses, have been published.[9-11]

Despite this growth and consolidation of resources, the need for even more information for physicians remains crucial, especially as the number and size of various ethnic groups in this country continue to grow. This issue describes the special needs of immigrants and indigenous groups in the United States today and ways that clinical medicine and social sciences can combine to address these needs.

Ethnicity

The US Census Bureau refers to various subpopulations or groups in the United States as "races," a classification based on outmoded concepts and dubious assumptions about genetic difference. In fact, race is poorly correlated with any biologic or cultural phenomenon other than skin color, which makes it a useless classification for biomedical or social research.[12,13] Census figures give some idea about the size of groups from specific nations or regions, but such figures do not necessarily reflect the size—or existence—of specific distinct groups, such as the Mien from Laos or Cambodia in Southeast Asia. Unlike race or national origin, ethnicity is a sociologic construct that is highly correlated with behavioral and cultural phenomena, particularly language, dress, adornment, food preference, religion, patterns of social interaction, choice of marriage partner, and family composition. Thus do the Mien and Gypsies in California constitute ethnic groups.

Special Issues Compared—1983 and 1992

Like the 1983 version, this special issue of *WJM* recognizes the need for more accessible, timely, and relevant work on cross-cultural issues in medicine. Both volumes aim at introducing a broad range of ideas, issues, and populations to clinicians and medical social scientists and at enticing them both to delve further into the available resources on cross-cultural medicine and to expand the literature through research and writing.

This issue does not supercede the earlier volume, whose articles are still relevant and worthy of study; rather, this special issue is a companion to the 1983 one. Although far from comprehensive, between the two special issues the most sizable ethnic populations in the contemporary United States are covered, and some pressing medical or health issues are raised concerning those groups and their relation to biomedicine.

In both volumes the focus is on groups situated in the United States or subject to US government oversight. Populations outside this country and the huge amount of cross-cultural health and medical research being done abroad by American and other social scientists or physicians are excluded—not because such work is unimportant or unable to illuminate issues for a domestic audience but, in part, because it is so vast. Similarly, work being done in the biophysical domain is not represented here. Again, the reason is not that such work is irrelevant to clinical medicine but that it is wide in scope and worthy of more than token representation.

From the Medical Anthropology Division, Department of Epidemiology and Biostatistics, University of California, San Francisco.
Reprint requests to Judith C. Barker, PhD, Department of Epidemiology and Biostatistics, UCSF, Box 0850, 1350-7th Ave, San Francisco, CA 94143.

The 1992 special issue differs from the 1983 version in several important ways: The specific populations covered, topics discussed, social science approaches represented, and authors have all undergone some change.

Groups Covered

In this issue are discussed ethnic or population groups that are mostly different from those examined in 1983. Not all ethnic populations in the US are covered, but the major groups (in terms of absolute numbers) are well represented, with a few notable exceptions (Thai immigrants, for example), largely because we were unable to find people to cover the topics or groups adequately in the time available.

Minority groups or those with a long history in the United States have more coverage than have smaller or newer groups. At least five articles refer to Hispanics, and four discuss African Americans. Immigrant or refugee groups, such as Afghans, Iranians, East (Asian) Indians, Ethiopians, Koreans, Vietnamese, Mien (Laotian), and Chinese are introduced, as are indigenous ethnic groups, such as urban American Indians. Asian populations, so often clumped together under the broad and nearly meaningless rubric "Asian and Pacific Islanders" and so often treated as equivalent units, have been dealt with separately. Groups that are often forgotten or overlooked because they are thought to be small in number or because many people simply do not realize that they exist are included here, such as Gypsies.

As Clark noted, refugees and immigrants often have special medical problems, such as higher rates and different types of infectious diseases, more problems with parasites, and greater experience with extreme stress and disruptions in the life course.[1] They frequently are socioeconomically disadvantaged, have poor English-language skills, and are subject to discrimination. Most refugee and immigrant populations are young, making maternal and child health prime areas requiring attention. Most come from pluralistic societies with different (and sometimes multiple) standards of conduct and different symbols, rituals, beliefs, and values. Individual members of any social group differ from each other, and often socioeconomic and educational differences can outweigh ethnic or cultural ones. Refugees and immigrants, especially those from rural areas, are sometimes not at all familiar with biomedicine but rather orient themselves toward their close-knit families who are the primary caregiving and decision-making units.

Topics Discussed

Although the range of medical specialties covered is wider than in 1983, some specialties such as neurology, ophthalmology, orthopedics, and surgery are still not represented, largely because ethnic or cultural issues have not yet been investigated with respect to these areas. Virtually all the articles are relevant to family practitioners or internal medicine, although chapters are included that will appeal specifically to psychiatry or mental health, obstetrics and gynecology, infectious diseases, oncology, health education, occupational health, and geriatrics.

Examining and understanding the fundamental health beliefs and values of different groups have long been of central importance in medical anthropology and cross-cultural medicine. Health beliefs—ideas about illness and healing or explanatory models[14]—are important because they provide an explanation for and assign a rational basis to otherwise unpredictable and abnormal events with potentially serious consequences and they provide criteria for judging if a person is sick and how to respond to various categories of sickness.[1] Frequently health beliefs focus on several dimensions simultaneously, for instance, on both proximate and distant causes of an abnormality. The focus is usually on issues larger than mere disease; for example, the incorporation of a spiritual dimension, such as illness being punishment for sin, is common. Although many people exhibit pragmatic attitudes toward therapy, happily using any treatment thought capable of offering relief or cure, basic beliefs about the cause and meaning of illness are frequently resistant to change.[1]

When the basic belief structure of biomedicine and another set of health beliefs differs radically, problems and frustrations almost inevitably arise. For instance, minority patients might be described as "noncompliant" by clinicians (who, mainly, have been socialized in a white urban middle-class milieu) when, in fact, the patients are "following the rules," but rules that are based on a different set of principles.[15]

In addition to basic health beliefs, other commonly discussed topics such as mental health, medical pluralism, and the organization and delivery of services appear in this issue, as do various new topics: for example, breast health, bioethics in the context of life-support technologies, the occupational health of farm workers, the acquired immunodeficiency syndrome, the use of translators, national differences in basic clinical conceptualizations, disclosing "bad news," and health policy with respect to the elderly. Some current issues in biomedicine that are likely to generate diverse and strong responses in various ethnic groups are omitted, largely because there is not yet an adequate literature or research base for discussion. Such issues include organ transplantation, fetal surgery, reproductive technology, access to health insurance, and education and employment of foreign-born health professionals.

Types of Social Science Represented

The basic approaches that authors have used vary widely—ethnography, case study, event analysis, survey, epidemiology, literature review, and analysis of national data sets. All these approaches have their place, and all contribute to our understanding of these complex issues. No one approach is comprehensive, however. In the long run, applying several different styles of data collection and analysis to a particular issue will result in greater understanding than will any one approach at the exclusion of any other.

We seem not yet to have life histories or phenomenologic studies of illness as experienced by people outside (mainly) the white urban middle-class—that is, by ethnic, especially immigrant, populations. Absent, too, are social histories of the experience of changes in health status, of alterations in health beliefs and practice, and in the organization and use of services.

Recently the National Institutes of Health took an important step in insisting that any clinical investigations they support include, where appropriate, minority populations, women, and the aged. What must be vigorously guarded against, however, is a new "tokenism." To investigate a minority population adequately with respect to either basic psychosocial processes or clinical responses demands rigorous attention to sample size and composition. However large, an aggregate of nonwhites—a few Chinese here, a couple of

African Americans there, and a Hispanic or two—does not a proper sample make.[12,13]

The amount and scope of work still needing to be done in cross-cultural medicine are enormous. Continued research is vitally necessary.

Authors

Cross-cultural medicine is not the preserve of any particular academic discipline or mode of scientific inquiry, as the authors of these articles show. They represent a wide range of backgrounds, from clinical medicine, through public health, policy science, and administration, to the various social sciences (mainly but not exclusively anthropology).

In an important way, this issue differs from the 1983 one. In the current one, at least a third of the authors are members of the ethnic group about which they write. Altogether, authors from at least seven different minority populations are represented. As in the 1983 issue, one minority group is well represented among authors—women make up at least half the contributors.

This change points not only to the success over the past 15 years or so, but also to the continued need, of efforts to recruit, train, and deploy minority scholars in all academic disciplines and professional fields. These minority scholars contribute an invaluable perspective that greatly enhances understanding, a perspective regrettably still largely absent in medicine or social science.

The greater number of multiauthored papers in this issue compared with the 1983 one is an indication of a growing trend toward collaborative multidisciplinary research in cross-cultural medicine. Although authors from the San Francisco Bay Area dominate the list of contributors, about half the contributors come from other parts of California, elsewhere in the country, or even overseas. The dominance of California authors is not surprising, given the heavy concentration and long duration of medical social science interests there, especially in the San Francisco Bay Area, and given the rapidity with which the size of the foreign-born and minority portion of the state's population has grown in the past decade.

Major Themes

Generally, within its particular topical focus, each paper addresses more than one theme. Taken overall, several major themes emerge.

Within-Group Diversity

A common assumption is that immigrant and other ethnic groups are monolithic and uniform in belief and behavioral norms. Such an assumption leads to simplistic and unwarranted ideas about ethnicity, even to the stereotyping of cultural heritage.

Several authors in this issue—Beyene, Gold, Lipson and Omidian, Kramer, Ramakrishna and Weiss, Wallace and Lew-Ting—allude to the existence of within-group diversity in the groups about which they write. Religion, education (frequently reflected in income and occupation), location (rural versus urban), and sex (male versus female) are key social factors creating diversity in specific groups. Cohort, history, and socioeconomic class are other powerful factors creating heterogeneity. For immigrant groups, the length of residence in the United States and facility with the English language also have great power to stratify the population into sectors with varying success at adjusting to American life, the health care system, and the economy.

Central Role of the Family

The family is an important player in the making of many decisions, health-related and otherwise (see Beyene, Bowser, Brod and Heurtin-Roberts, Gold, Muller and Desmond, and Sutherland). In many non-EuroAmerican families, family business, especially "secrets," is kept from the outside world, but among family members there is greater openness (Ramakrishna and Weiss). Decision making, the receiving and disclosure of news, and the orchestrating of care are key concerns and responsibilities of the group, not the individual—Beyene, Ramakrishna and Weiss, Wallace and Lew-Ting.

Problems can abound if roles are reversed, especially within immigrant families. This can occur when children are put in a position of authority over parents or older adults, such as when they are asked to translate during medical encounters because they understand or speak English better than the older generations (Haffner, Sutherland), or when husbands lose authority within the family because they cannot find sufficient work but their wives can (Gold, Lipson and Omidian). An awareness of cultural values about the social role of women, sexuality, and the meaning of marriage is important to understanding some causes of and responses to disease (Bowser, Gates-Williams and associates, Mo, Ramakrishna and Weiss). In immigrant groups, intergenerational relations, especially between parent and child or grandparent and grandchild, can be restructured and strained when children through their exposure to school become more quickly acculturated to American life (Gold, Ramakrishna and Weiss).

Physician-Patient Relationship

Disclosure of personal information, including current symptoms or health history, by a patient is not always appropriate on first meeting a new health care practitioner—Beyene, Chin, Kramer. Reticence and shyness allow a person to judge how sympathetic a clinician will likely be when "real" health concerns are eventually disclosed. An ethnographic approach to eliciting medical histories from ethnic patients might produce more relevant information than the more traditional style of questioning in biomedicine (Gold, Kramer).

Mental Health

Do not underestimate the long-term effects on mental health of historic events or processes such as generational or spousal role reversals, or political upheaval and war. Depression, apathy, and somatization of mental anguish can easily result (Chester and Holtan, Gold, Lipson and Omidian).

Expressing emotion in culturally appropriate ways, particularly deep emotions of grief, fear, and rage, is not always understood by American health care professionals—Beyene, Pliskin. Not all emotions are openly expressed, nor can they necessarily be talked about (Pliskin). The value of the "talking therapies" such as psychiatry is not always appreciated (Brod and Heurtin-Roberts).

Torture is so destructive of a sense of a personal, social, or cultural self that, no matter their background or country of origin, all survivors of physical torture and extreme psychological terror express their pain and suffering in the same basic way—they become acclimated to a "culture of torture"

with values that persist long after the physical and psychological abuse has stopped (Chester and Holtan). In the past decade, many more refugees have arrived in the United States from war-torn lands and from nations that authorize torture as a means of political control. No physician in a major US city can any longer be surprised at finding torture survivors in his or her practice. It is imperative to understand and treat appropriately such special patients.

Bioethics

Much of modern medical practice is laced with land mines because it is predicated on the assumption that the person experiencing illness is the one to make health care decisions and who has a right, indeed almost a duty, to be told the diagnosis and prognosis. Ideas like autonomy, independence, and competence undergird communication processes and the physician-patient relationship. Serious questions can be raised about the appropriateness of these assumptions, especially when dealing with immigrant or other groups with cultural values vastly different from those underpinning biomedicine (Beyene, Klessig, Muller and Desmond, Ramakrishna and Weiss).

Bioethics is still largely entangled in asocial, acultural, and decontextualized philosophical, moral, and legal discourses. It has yet to investigate comprehensively the social and cultural realities that matter to diverse patient populaces. Physicians, legislators, health economists, and policy analysts debate the use of heroic or "high-tech" procedures for frail elders.[16] Older adults themselves, however, generally reject such costly death-defying measures and yearn for far less expensive items—such as a telephone next to a nursing home bed or someone to go grocery shopping for them when they are homebound—that would enhance significantly the quality of their remaining life.[17]

There are fundamental differences in the way biomedicine and certain ethnic people conceptualize the role of the sick person and family in medical encounters (Beyene, Klessig, Muller and Desmond). The meaning of "hope"[18] and the relative importance of diagnosis to prognosis for various cultural groups need be paid much closer attention.

Medical Pluralism

Some health professionals feel insulted and distressed when patients seek or use other cures or therapies, often dismissed as "folk medicine." Not all alternative healing systems are ineffective; some can alleviate physical symptoms, and many address psychosocial issues ignored by biomedicine (Chin, Gilman and colleagues, Ramakrishna and Weiss). People of other cultures think that Western medicine is not always capable of curing or alleviating particular disorders or conditions, especially those caused by spirits, ancestors, or behavioral impropriety. Often Western medical treatment and alternative or native therapies are not viewed as mutually exclusive endeavors (Chin, Gilman and co-workers). No matter how acculturated a person appears, at times of great stress, such as illness or death, early-learned ideas resurface and structure responses (Beyene, Bowser, Chin). Herbal medications are not necessarily ineffective or "harmless" (Chin, Gilman and associates). The potential for overdose, improper use, and drug interaction is real.

Biomedicine Itself

Biomedicine is often thought to be a uniform, monolithic science wherever it is practiced. Several articles effectively demolish this idea (Feldman, Ramakrishna and Weiss). Biomedicine has variant forms depending on where it is practiced: India is different from France, and France is different from the United States. Not only are the organization of service provision and the physician-patient relationship different, but so, too, are some basic conceptual and theoretic ideas that underlie the approach to treating disease.

Prevention

The concept of preventing disease is not always understood. Many immigrant groups, especially those with little previous exposure to Western medicine, find the idea novel (Brod and Heurtin-Roberts, Mo). In contrast, health belief systems based on ideas of balancing opposing forces, such as the Chinese *yin* and *yang*, East Indian *Ayurveda*, or other humoral systems, give a set of principles on which to monitor diet and behavior and thus to prevent the excesses that cause disease (Haffner, Ramakrishna and Weiss).

Policy

How do conceptualizations of disease and sociodemographic processes result in health policy and in the organization and provision of services? Some fundamental concepts of health policy and research and health education need to be revamped (Bowser, Gates-Williams and colleagues, Wray). Models developed mostly for urban white middle-class Americans are inappropriate for rural, remote, or culturally different populations (Gates-Williams and co-workers). Increasing ethnic diversity is calling into question the adequacy of health policies designed for specific age groups, such as the elderly (Wray).

Urgent reform of health and safety policies—and enforcement of existing codes—is needed for specific occupations that rely on the labor of ethnic workers, such as farm workers (Mobed and associates, Palerm). That poverty and ill health abound in wealthy rural areas is shocking. That poverty and ill health are still so strongly related to being non-white or a member of a minority group is an indictment.

TABLE 1.—*Composition of United States Population, 1990, and Percent Change, 1980–1990**

Population	US Population, 1990 No.	US Population, 1990 %	Change From 1980, %
Total	248,709,873	100	10
Race†			
White	199,686,060	83	6
African American	29,986,060	12	13
Native American	1,959,234	1	38
Asian and Pacific Islander	7,273,662	3	108
All other	9,804,847	4	45
Hispanic origin‡	22,354,059	9	53

*From the Bureau of the Census, Economics and Statistics Administration, US Department of Commerce.[19]

†Race does not denote any clear-cut definition of biologic stock but rather is a self-classification by people to the race with which they most closely identify.

‡Hispanic origin denotes origination of Spanish-speaking people from the Caribbean, Central or South America, Spain, or elsewhere. It is distinct from race; thus, persons of Spanish or Hispanic origin may be of any race.

Population Growth and Diversification—1980 to 1990

In the past decade in the United States there has been a 10% general increase in total population, but some groups grew considerably faster; for instance, the number of Asians and Pacific Islanders doubled (Table 1).[19] Through processes

of natural increase, groups with a long history in this country continue to grow at modest rates in all regions (Table 2).[19,20] African Americans are most numerous in the South, where some 15 million reside. The number of Native Americans, which includes Eskimos and Aleuts as well as American Indians, is relatively small—less than 2 million total—and they live predominantly in the West. Although Hispanics, totaling 22.3 million, reside in all regions, the origin of this population varies considerably by region: Cubans live mainly in the South, Puerto Ricans in the Northeast, Mexicans in the West and South, and all other Hispanics (those from Nicaragua, El Salvador, and Guatemala, for instance) are dispersed across all regions, with the fewest in the Midwest. United States-domiciled populations from the Pacific Islands have small population sizes compared with other groups, especially in regions other than the West. Micronesian and Samoan populations show more growth in each region (34% to 188%) than do Hawaiians (−3% to 28%). The influence of undocumented immigrants on population composition and size is unknown but is a concern especially for Hispanic populations.

Newer immigrant populations from Asia generally show much greater rates of increase over the decade (41% to 2,446%) and considerable variation in population size by region—for instance, for the Hmong: from 1,731 in the Northeast to 49,564 in the West. In Table 2, Asian groups are presented in order of total population size, from 1.6 million Chinese to 91,000 Thai. Smaller Asian groups have also been identified: 80,000 Pakistani, 30,000 Indonesians, 10,000 Bangladeshi, 10,000 Malayans, and 10,000 Sri Lankans, as well as some even smaller groups—6,000 Burmese and 2,000 Okinawan.[19] Detailed analyses are available of the

TABLE 2.—*Distribution of Specific Groups in the United States, 1990, and Percent Change in Those Populations, 1980 to 1990, by Region**†

	Population by Region‡§									
	Northeast		*Midwest*		*South*		*West*		*Total*	
Population Group	*No.*	*Change, %*	*No.*	*Change, %*	*No.*	*Change, %*	*No.*	*Change, %*	*No.*	*Change, %*
Total	50,809,229	20	59,668,632	24	85,445,930	34	52,786,062	21	248,709,853	10
African American	5,613,222	16	5,715,940	7	15,828,888	13	2,828,010	25	29,986,060	13
Native American	125,148	--	337,899	--	562,731	--	933,456	--	1,959,234	38
American Indian	121,551	59	333,998	36	557,214	51	865,522	29	1,878,285	38
Asian and Pacific Islander	1,335,375	--	768,069	--	1,122,248	--	4,047,970	--	7,273,662	108
Total Asian	1,324,865	--	755,403	--	1,094,179	--	3,734,191	--	6,908,638	347
Chinese	445,089	105	133,336	83	204,430	124	862,617	103	1,645,472	105
Filipino	142,958	91	113,354	42	159,378	86	991,080	85	1,406,770	82
Japanese	74,202	58	63,210	42	67,193	41	642,457	14	847,062	21
East (Asian) Indian	285,103	136	146,211	72	195,525	116	188,608	162	815,447	126
Korean	182,061	167	109,087	76	153,163	116	354,538	130	798,849	125
Vietnamese	60,509	144	51,932	42	168,501	119	333,605	178	614,547	135
Cambodian	30,176	1,222	12,921	472	19,279	650	85,035	853	147,411	819
Hmong	1,731	390	37,166	1,237	1,621	1,218	49,564	2,446	90,082	1,631
Laotian	15,928	241	27,775	108	29,262	273	76,049	249	149,014	213
Thai	11,801	64	12,981	54	23,747	133	42,746	120	91,275	102
Total Pacific Islander	10,510	--	12,666	--	28,069	--	313,779	--	365,024	42
Hawaiian	4,135	−3	5,534	1	12,240	7	189,105	28	211,014	27
Samoan	1,503	188	2,243	81	4,055	127	55,163	46	62,964	50
Micronesian‖	3,683	60	3,358	34	8,676	57	36,027	43	51,744	54
Hispanic Origin	3,754,389	44	1,726,509	35	6,767,021	51	10,106,140	62	22,354,109	53
Mexican	174,996	--	1,153,296	--	4,343,523	--	7,824,123	--	13,495,938	54
Puerto Rican	1,871,981	--	257,594	--	405,941	--	192,238	--	2,727,754	35
Cuban	183,636	--	36,577	--	735,458	--	88,261	--	1,043,932	30
All other Hispanic	1,523,776	--	279,042	--	1,282,099	--	2,001,518	--	5,086,435	67
Refugees, 1983–1991¶#										
Afghan	4,684	475	1,092	425	4,982	627	8,875	722	19,633	582
Ethiopian	2,679	759	2,770	694	7,961	741	6,833	632	20,243	695
Iranian	5,917	3,360	1,482	2,180	4,275	1,996	22,275	4,680	33,949	3,647
Russian**	75,984	10,366	18,354	13,395	12,608	11,908	47,847	11,319	154,793	11,068

*From Bureau of the Census, Economics and Statistics Administration, US Department of Commerce.[19]

†The US Census Bureau calls these "racial groups," not cultural or ethnic groups. They are essentially aggregate figures for people who originated in a particular country or region, or are affiliated with such a group. For example, people of Thai origin could be from any one of a number of different groups, such as Karen or Luo, that are culturally distinct. Micronesians could be from separate countries such as the Republic of Palau, Guam, the Federated States of Micronesia, or the Marshall Islands, but nevertheless share certain central cultural characteristics. Chinese does not distinguish between Chinese born in the United States, ethnic Chinese from Vietnam, and those recently arrived from, for instance, Taiwan or Hong Kong.

‡As defined by the US Bureau of the Census, 1990, regions comprise the following states: *Northeast:* Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; *Midwest.* Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin; *South:* Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia; *West.* Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming.

§-- = not available.

‖Micronesian data are the sum of data given separately for Guamanian, Northern Marianas, and Palau.

¶From unpublished information from the Refugee Resettlement Program and from Office of Refugee Resettlement.[20]

#These populations are not enumerated separately in the US Census and therefore are included in the above figures. These data are given here so some idea can be gained of the size, distribution, and change (increase) in these populations relative to groups that are enumerated. Refugee figures refer to numbers admitted from a particular country of origin at a specified time period. They do not account for any increase in population since the year of resettlement. Thus, to an unknown degree, these figures underestimate the size of the population.

**The terms "Soviet" and "USSR" were widely used throughout the Refugee Resettlement Program's Report (unpublished). This corresponds to Russian as used in this issue of THE WESTERN JOURNAL OF MEDICINE

factors "pushing" and "pulling" various Asian and Pacific populations to the United States, of the heterogeneity within such groups, and of the consequences of migration for such groups.[21]

Immigrants come to this country primarily for one of four reasons: education, economic benefit, family reunification, and escape from political oppression or war (as persons seeking asylum or refugees). The greatest increases in population from 1980 to 1990 are among groups able to enter as refugees (see Table 2)—that is, among Southeast Asians (such as Cambodian and Hmong), Middle Easterners (such as Afghan and Iranian), Africans (such as Ethiopian), and Eastern Europeans (such as Russian).

Refugees

The exact size and location of many non-Southeast Asian refugee populations are difficult to determine because the US Census Bureau does not enumerate them as distinct groups. Refugees from Eastern Europe and Ethiopia, for instance, are most likely included in the census under the categories white and black, respectively. Refugees are sometimes enumerated by agencies other than the US Census Bureau and for different purposes.[20,22-24] Reconciling the difference in numbers among agencies is not always easy or possible; official documents claim that just over 20,000 Ethiopians entered the United States between 1983 and 1991, yet a 1990 survey estimates the population of Ethiopians to be between 50,000 and 75,000, with 6,000 arriving annually.[23] Similarly, estimates place more than 100,000 Afghan refugees in the United States in 1988,[24] although official figures document only 19,600.[20]

Several factors lead official counts of refugees to be (sometimes severe) underestimates of population size. First, counts of these populations refer only to those entering as refugees and do not include people entering under other immigration statuses who later acquire permanent residency. Often, too, they do not include those seeking asylum or refugees who enter the United States under private (such as church) sponsorship. Further, these figures refer only to a specific time of entry. They do not account for natural increases among these generally young populations over the decade.[22] Thus, caution should be exercised when population figures referring to refugees are interpreted.

Despite the problems with counting non-Southeast Asian refugees, it is obvious that all regions have experienced phenomenal growth—in the 10,000% range—in the Russian (people from the former USSR) refugee population since 1981 (see Table 2).[20] This is at least five times the greatest growth rate for any other group. Unlike most other refugee and immigrant groups, which comprise mainly young adults aged 25 to 34 years, a substantial proportion (around 10%) of Russian immigrants are aged 65 years or older.[20] Russian refugees are a challenge to resettlement organizations because they are not accustomed to providing for large numbers of newcomers with such demographic—and, consequently, social service and health—characteristics.

Western Region

The Western region is home to just more than a fifth (21%) of the total population of the United States. Yet the West is experiencing population growth and diversification on a far greater scale than any other region. As Table 3 shows, for only two minority groups enumerated by the US Census—African Americans and East Indians—is less than 40% of the population resident in the West.[19,20] Official statistics on refugee populations reveal that two groups—Ethiopians and Russians—settle predominantly outside the West.

California

Most of the West's population resides in a single state—California. In only five specific groups does less than 50% of that population for the entire Western region live in California; in 17 instances, more than 70% of specific populations lives there (see Table 3).

Consistently since 1983-1984 California has received more than 30% of all refugees to the United States; in 1987-1988 the proportion reached 46%.[22] Until 1986-1987, Southeast Asians were the majority of refugees to California; now refugees from elsewhere outnumber the continuing stream of refugees from Southeast Asia. By 1988-1989, Russians constituted 58% of all non-Southeast Asian refugees entering the state.[22]

Not every county, city, or community in California is affected equally by immigration. The Los Angeles-Long Beach and the San Francisco Bay areas were, respectively, second and third in the nation (behind New York City) in receiving foreign immigrants in 1988-1989.[25] Southeast

TABLE 3.—*Proportion of 1990 United States Population in the West and Proportion of Western Region's Population in the State of California**

Population Group	Proportion of 1990 US Population in the West, %	Proportion of West's Population in California, %
Total	21	56
African American	9	78
Native American	47	26
American Indian	46	27
Asian and Pacific Islander	56	70
Total Asian	54	73
Chinese	52	82
Filipino	71	74
Japanese	76	49
East (Asian) Indian	23	85
Korean	44	73
Vietnamese	54	84
Cambodian	58	81
Hmong	55	95
Laotian	51	76
Thai	47	75
Total Pacific Islander	86	35
Hawaiian	90	18
Samoan	88	58
Micronesian†	50	72
Hispanic Origin		
Total Hispanic	45	76
Refugees, 1991		
Afghan	45	84
Ethiopian	34	67
Iranian	66	94
Russian‡	31	77

*From the US Bureau of the Census, Economics and Statistics Administration, US Department of Commerce[19], unpublished information from the Refugee Resettlement Program; and the Office of Refugee Resettlement.[20]

†Micronesian data are the sum of data given separately for Guamanian, Northern Marianas, and Palau.

‡The terms "Soviet" and "USSR" were widely used throughout the Refugee Resettlement Program's Report (unpublished). This corresponds to Russian as used in this issue of THE WESTERN JOURNAL OF MEDICINE

Asian refugees, refugees from elsewhere, other legal immigrants, and undocumented ones continue to pour into these two metropolitan areas. But it is not only urban areas in California that are experiencing population diversification: In 1989, three counties in the rural San Joaquin Valley had the highest ratio of Southeast Asian residents per 1,000 population (San Joaquin 70, Merced 59, and Fresno 56).[22]

The size and distribution of California's ethnic populations are affected by primary migration from abroad and secondary migration from other parts of the United States. Secondary migration accounted for 45% of the increase in California's Southeast Asian populations in 1988-1989.[22] Data on secondary migration of non-Southeast Asian refugees are not available, but agency and anecdotal reports suggest this is common. Ethiopians, for example, are moving into California from other parts of the country, in part because of the large Ethiopian population already in Los Angeles and the San Francisco Bay Area, which allows for better community formation and economic opportunities, and in part because the climate is similar to that in the homeland (Beyene, oral communication, July 1992).

Conclusion

Cross-cultural medicine is challenging, frustrating, exhilarating, and rewarding. The need for sensitivity to cultural issues as they impinge on the practice of the healing arts will only increase in the coming years, as population diversification continues. It is our hope that this special issue will assist clinicians to be more effective in their relations with ethnically heterogeneous patients and to encourage both medical social scientists and clinical researchers to expand their research activities into areas of concern to diverse cultural groups.

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Cross-cultural Medicine
A Decade Later

Translation Is Not Enough
Interpreting in a Medical Setting

LINDA HAFFNER, *Stanford, California*

This article is based on speeches given in January and September 1991 at conferences sponsored by the Mid-Coastal California Perinatal Outreach Program.

Unique obstacles must be overcome when providing medical care to patients who have an incomplete command of the English language. Serious barriers to effective communication may arise at the exact point where our health care system must succeed or fail. Miscommunication, differences in attitudes about health care, and various other misunderstandings interfere with or frustrate good health care for these patients and their families. Such difficulties are best overcome by the use of a professional interpreter who can ensure good communication between patients and health care professionals. My daily experiences as a professional medical interpreter and translator in Spanish provide insights into the complexities of bilingual and bicultural communication in the hospital setting. Although the examples given relate to Hispanic patients, the lessons learned can be extended to other foreign language patients as well.

(Haffner L: Translation is not enough—Interpreting in a medical setting, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:255-259)

Health care professionals often experience communication difficulties with Spanish-speaking patients; some also have various misconceptions about these patients. As a professional Spanish-language interpreter and translator* at Stanford (California) University Medical Center and being from Nicaragua, I know the problems these patients have in the clinics and the hospital wards. In this article I invite readers to accompany me on a typical day and to share some of these experiences. Some of them are sad, some are amusing, and all are interesting. If they counter a misconception or provide some small insight, I will have been successful.

Before I describe a typical day in my profession, I must point out that not all Spanish-speaking patients are the same. They come from different cultural backgrounds, cultural influences, and educational levels.[1] Highly educated and affluent Latinos† have attitudes and beliefs about health care reasonably comparable to those of similarly educated and wealthy Americans. The challenge, and the subject of this article, are the Hispanic patients who are poor, come from rural areas, have little or no schooling, and have little or marginal fluency in English. These patients frequently but not necessarily are migrants or recent immigrants.

Cultural Issues

My day begins at 8:30 AM. When I arrive at the hospital, three messages are already waiting for me on my beeper. The first is from an anesthesiologist in the Delivery Room who needs me to translate his explanation of the epidural procedure. An 18-year-old Mexican patient is having regular contractions, but she is only 4 cm dilated. The patient is becoming tense and exhausted from the pain, which is interfering with the childbirth process. The nurse has suggested some pain relief medication or an epidural block, but the patient refuses.

As I clarify the nurse's offer to the patient, I learn the patient's real concern. She thought that she was being offered a *raquea*. *Raquea* or *raquidea*, a term frequently encountered in patients from rural Mexico, refers to the anesthesia procedure commonly known in the United States as a spinal block. Mexican patients associate *raquea* with a high incidence of serious complications. This patient is afraid that she would have chronic back problems or be paralyzed for life if given the *raquea*, problems she believes are caused by that procedure. To make it worse, at this moment her husband reminds her that if she does not have pain, she will not be a real mother, a common belief among Mexican patients. We explain to the patient that the epidural block is not like the *raquea*, that she would be awake and able to push and actively participate in her baby's birth. Finally, the husband and the patient agree to the epidural, and the baby is born without complications. The problem here is the patient's expectation that medical practices in the United States are the same as in Mexico and her fear (justified or not) about those medical practices, all complicated by basic cultural differences and beliefs. By creating in the patient a better understanding of

*Although these terms are often used interchangeably, technically interpretation involves oral communication and translation involves written communication.

†In this article the terms "Hispanic" and "Latino" are used interchangeably to refer to persons who are Spanish speakers and whose principal cultural identity is Latin American.

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the epidural procedure, we are able to bridge the language, cultural, and knowledge gaps.

By around 9 AM the Obstetrical Diabetic Clinic is active. Each patient is seen by a physician, the hospital's dietitian, a social worker, and the nurse in charge of drawing blood. An interpreter is needed for almost every interaction. One patient, Ramona, is being seen for the first time in this clinic. She is 34 years old, Central American, and poor. She is a first-generation immigrant and, as is typical, believes herself to be a transient by choice. She has the idea that she will return to her country someday and has not committed herself to becoming part of the Anglo culture. "I would learn English if I planned to stay," is a common comment. Her command of English is exhausted after a few simple words and smiles.

As I go into the room, I recognize her from another clinic in the hospital, and we greet each other by name. As part of her medical history, she is asked how many pregnancies she has had. She responds, "two." I continue to interpret for the physician as he asks all the different questions connected with her history. Ramona and I talk a little in Spanish while the physician makes some notes. Latino women, once they get to know you, tend to be talkative. She tells me how worried she is about her diabetes, which she believes she probably caused herself by "doing something wrong."

She tells me about a third pregnancy that miscarried due, in her mind, to *susto*. *Susto* means "a terrible fright," and she holds the common belief that a terrible fright during pregnancy is bad for both mother and baby and can even kill an unborn child. She explains that, while pregnant, she was taking care of a 15-year-old niece. Suddenly the young girl felt sick to her stomach, went to bed, and died on the spot. Our patient had been terrified and had felt responsible. To make matters worse, the girl's family blamed our patient for the girl's death. The patient was about four months' pregnant at the time and miscarried four days after the incident.

On hearing her story, I realize that she actually has had three pregnancies, not the two she had stated in response to the physician's question. For many Hispanic women, having a miscarriage or a stillborn child does not equate with a pregnancy; only the successful pregnancies count. In this example, the patient answered the physician correctly in the context of her cultural views, but, through no fault of his own, the medical history he obtained from this patient was incomplete. Her different cultural attitudes and beliefs are discovered and better understood through our conversation, and a more accurate and complete history results after those beliefs and attitudes are taken into account.

At 9:25 AM there is a knock at the door as I finish up with Ramona, this time from the dietitian. The dietitian explains that a patient needs to be put on a special diet for diabetic pregnant mothers, to see if her diabetes could be controlled without insulin. This is a major task of persuasion. There is a saying in Spanish, *"Dame gordura y te daré hermosura"* ("Give me plumpness and I'll give you beauty"). This idea applies to babies, too. The belief is that a pregnant mother has to eat for two, that a thin baby is undesirable because a thin baby is unhealthy.

In addition, many of these patients come from poor rural areas where most of their food is scarce and expensive, where meat is a luxury, and where anything American-made is beyond reach. When these patients come to this country, where food is abundant and comparatively cheap, they naturally tend to indulge. They have difficulty understanding that they should voluntarily go on a diet of restricted foods in the land of plenty. This patient believes in having a big baby, and she enjoys being able to eat anything she wants. We finally convince her that she cannot do this any longer and that, for the sake of her health, she has to diet to have a smaller baby.

Often there is another complication if the family has little money to buy food. The diet we recommend, lots of vegetables and less tortillas and beans, typically is more expensive than what these patients otherwise would eat. It is also less popular because it omits the foods they like the best. The surprising result is that there are fewer compliance problems than would be expected, even with all these frustrations. Having a baby is important to Hispanic women, so most of them overcome their reluctance and comply with the recommended diet or at least try their best with their limited resources. In the Latino culture, women are supposed to sacrifice for the family, even to the point of eating a lot of vegetables.[1,2]

My next summons is from the Internal Medicine Clinic. The patient, a 50-year-old female peasant from Mexico, is accompanied by her 35-year-old son. Although the patient has been coming to the clinic for some time, she is new to me. Her son usually interprets, as he is reasonably fluent in both languages. This time I am called because the son has to leave to go to work.

Before going into the room, the physician expresses to me his concern about whether the health problems claimed by this woman are real or imagined. She has been in the clinic three times before, each time with different vague and diffuse complaints, none of which make medical sense. As we learn, the poor woman has a fistula in her rectum. In her previous visits, she could not bring herself to reveal her symptoms in the presence of, and therefore to, her son as he interprets for her. She tells me that she has been so embarrassed about her condition that she has invented other symptoms to justify her visits to the physician. She confesses that she has been eager to have a hospital staff interpreter from the first visit, but her hope had not materialized until now.

This story illustrates two things: first, the modesty of many Latino women can be a serious problem; second, Latino women are often reluctant to reveal personal or private problems if their children are used to interpret. I have seen many Hispanic women who are reluctant to tell their physicians about vaginal problems or to have a Papanicolaou smear done because they are afraid of a pelvic examination.[1] Their fear is partly caused by their expectation of discomfort, but to a large degree it is the result of a higher cultural standard of modesty. In addition, traditional Hispanic women often have an amazingly limited knowledge of female sexual anatomy. These attitudes may puzzle Anglo professionals but must be dealt with for medical care to be effective.

Using Children as Interpreters

My day is becoming hectic, and I am needed in several places at once. A common and unfortunate practice when an interpreter is temporarily unavailable is to use family members to interpret. It is easy to forget that the person in the middle is affected by what is happening and must assume a normal family role when the interpreting duties are over. The next page I answer involves this difficult and disturbing problem.

The call is to help with a pregnant woman who may have a stillbirth. As I enter the patient's room, the first thing I see is a beautiful little girl with haunting big brown eyes—the patient's 7-year-old daughter. I introduce myself with the proper Spanish salutation. The mother seems upset, but the daughter looks very distressed and frightened. The child is shaking and with a quiet voice says to me, *"No podía explicarle a mi mamá todo lo que los doctores me decían"* ("I couldn't explain to my mom everything the doctors were telling me"). I quickly discover that this little girl was used as the interpreter during the ultrasound examination and was told to tell her mother that the baby (her little brother-to-be) is dead. This revelation stuns me. I sit and hold the little girl on my lap, trying to comfort her as she hugs me tightly. I softly talk to her about what has happened, and she starts to weep with big, slow tears. To me, one of the saddest moments is when she says to me, in a pleading voice, "Maybe my little brother's heart will work when he comes out of my mother's stomach."

I am reminded of the time when I was required for a family conference for a patient about to be discharged. When I arrive at the conference, present are a physician, a nurse, a physical therapist, a social worker, and several family members. The patient, the father, is absent. Everyone is sitting around a table except one. Standing by the physician is the patient's 9-year-old son, who is acting as the interpreter. The child looks frightened. The physician rather abruptly says to me, "We don't need you, the boy is doing fine." The boy, however, pleads with me to stay and take over, saying, "Please, *Señora,* can you help me? I don't know if I am doing it right."

Having to rely on interpreters certainly can be frustrating at times. The communication is inevitably slower, more awkward, and less precise, even if the interpreter is excellent. Another source of frustration is that the health care professional has less control when having to use an interpreter (professional or otherwise), and some, understandably, have a hard time with this fact. There is a simple explanation: The physician and the patient cannot speak to each other directly. Also, there may be a wait before the interpreter arrives. Because of budgetary constraints, there never are enough interpreters on staff for there to be on-call interpretation available for every need. Medical interpretation often involves unexpected matters of life and death. Being an interpreter is a heavy burden for a child, whose English is frequently marginal and certainly is not sophisticated. Disregard for these factors is hurtful to both the child and the family and threatens the effectiveness of the communication. The trauma to the unfortunate little girl (whose mother has a stillborn) is easily seen. I doubt anyone would consider using a child in this way if there were no language barrier. The situation in which the boy was used as an interpreter is similarly difficult, but the difficulty is perhaps a little more subtle.

In rural Hispanic culture, the hierarchy is strict, with authority running from older to younger and from male to female. These relationships are for life, with parents in control of adult children and older adults in control of their younger adult siblings. Traditionally in Latino culture, the head of the family is expected to make the decisions regarding any family member. The whole family looks to this person for support and advice.[3] By using a young family member as an interpreter, the physician puts the child in control, with a much higher status than the child would otherwise have. This disrupts the family's social order.

In both of these cases, there was no emergency and no reason not to wait a few minutes for a professional interpreter to arrive. When foreign language gets in the way, however, otherwise sensitive and caring people occasionally become oblivious, and unintended harm can result.

Informed Consent

I am getting tired; it is nearly lunchtime, and the pages are relentless. This time I am called to the Well-Baby Nursery, where a woman needs to be asked about some routine matters: the family constellation, safety in the home, safety in the car, breast or bottle feeding, and follow-up care for her baby. Interpreting for the physician, I ask her whether she wants her baby boy circumcised. She nods, but then pauses and very seriously adds, "But my friend had a baby circumcised here, and they did it too much. I don't like how he looks. Can they just cut off a little bit?" To me, the woman clearly wants to decline the procedure but is having difficulty refusing what she considers an instruction from the physician. In general, Latinos feel they should agree with physicians out of politeness and respect, even when they really disagree or do not understand the issues involved. They expect physicians to make the decisions for them and do not understand why they are asked to make choices. They are used to, and seem to prefer, deferring to experts. These patients do not understand the American medical system and its notion of informed consent. Only when more acculturated do they start taking the level of responsibility for their own health that Americans routinely assume. Language and cultural issues once again are intermixed.

The next interpreting request, which comes from the Gynecology Ward, involves a different issue of informed consent. The patient, a seriously ill 71-year-old Nicaraguan woman, has been in this country only a few years. Her children have been with her day and night, never leaving her side. When I arrive, the patient's family is distraught. They request a conference with the physician out of the patient's presence. The physician tells the family that the mother is dying and needs radical surgery, but he emphasizes that the surgery would prolong her life only a little. The physician wants to tell the patient and to ask for her consent to the operation. The daughters are very upset and against saying anything to their mother. They beg me to explain that their mother has the right to have hopes, that she should not be told that she is going to die, and that a painful and difficult operation that may buy her only a little more time is cruel. The result is an impasse that looks to go on for several days. The daughters vigilantly watch their mother, guarding her from physicians, and hiding the truth from her. Eventually a compromise is reached, with the patient receiving an accurate but moderated version of the bad news. Here the problem is partly language barriers, but mostly it is conflicting cultural attitudes about how (or whether) bad news should be conveyed to patients.

I am convinced that the daughters would have lied to their mother about her condition (and tell the physician they did the opposite) if they were relied on to interpret. Hispanic families often try to hide the seriousness of the situation from ill relatives, especially if the patient may be dying. Instead, the patient is always given encouragement by the family with words like, "It is going to be OK," "You'll be out of here

soon," and "The doctor said that you'll be fine and on your feet again." These desires and cultural practices are directly opposed to the Western notion of informed consent and our practice of describing medical situations in frank, sometimes brutal, detail.

Next I am called to the Maternity Ward. A woman had previously signed a consent for an elective tubal ligation after her delivery and is scheduled to have the procedure in half an hour. The nurses noted that she seemed uncertain about the operation and wisely chose to call in an interpreter. It is quickly obvious that the patient has not fully understood that the sterilization is essentially permanent. A tubal ligation has been described to her as having her tubes "tied." She has consented, but with the idea that she can later change her mind—thinking the procedure is easily reversible. If her tubes can be "tied," she reasons, they can be "untied." She began to worry after asking a few questions to confirm her belief. She does not fully understand the answers in English but was having doubts. After I interpret the answers to her questions, she declines the procedure.

Many Latinos believe that the main purpose in life is to reproduce, to people the land. This idea is strong and deeply rooted in their religious beliefs, which must be acknowledged, respected, and understood if we want to comprehend their attitudes toward family planning. Another family planning complication in Latinos is that men can feel threatened by the sterilization of the women. They often believe that a woman who is sterilized or uses birth control is going to be unfaithful. Besides, in their eyes, maleness is proved by paternity, and their attitude is that a wife is no longer a complete woman if she cannot bear children.

Language Barriers

A patient in another room, a 30-year-old spunky but illiterate poor woman from Mexico, is hard working and proud. She is seven months' pregnant and has diabetes. Her diabetes is under control, and she is generally in good health, but she has complained of swelling and pain in her hands on previous visits. Sitz baths were prescribed so that the patient could have immersion therapy for her hands and arms. Because the physician knew some Spanish and the patient knew a little English, no interpreters were used on previous visits.

On this visit, the physician and the dietitian are concerned about the patient's unexpected weight loss during the previous week, and they decide to call for an interpreter to help find the cause. As we try to figure out what is going on, the patient asks me to tell the physician that her hands are still hurting, but she proudly adds that she has been very good about doing her sitz baths. She says, "They are very tiring, but I have been doing them for 20 minutes twice a day." I ask her to tell me what she was doing because I wonder how a bath could be so tiring. Very seriously, she explains she would fill the bathtub with water and get in and sit down. Then she would stand up, sit down, stand up, sit down, stand up, sit down—for 20 minutes at a time. No wonder she was tired!

I want to both laugh and cry. The image of this very pregnant woman intently doing deep-knee bends in the bathtub is comical, but her pride and sincerity are touching. If she had fallen, she could have suffered serious injury. Once again I realize how important good communication is and how risks can be increased by faulty communication.

Next I am called to the Emergency Department. When I arrive, the room is full of physicians and nurses. Among them is an x-ray technician busily taking an x-ray film of a man's leg. The patient, a 38-year-old Mexican gardener, had fallen out of a 10-ft high tree. After I introduce myself, the physicians and I ask the patient routine questions. The man keeps repeating, *"Mi canilla, mi canilla."* Somebody else in the room knew a little Spanish, which explains to me why the technician is taking x-ray films of the man's leg. I tell them that he means his wrist, which turns out to be broken. In most Spanish-speaking countries, *canilla* means shinbone and the use of *canilla* for the wrist is a little unusual—except in certain parts of Mexico where the word means wrist. Spanish technically is not divided into dialects, but the meaning of a word can vary by context or the region of the speaker.

I sometimes observe physicians and nurses who know a little of the language trying to converse in Spanish with their Hispanic patients. I always encourage this practice. Among other benefits, it helps make a patient feel more comfortable and builds rapport.[4] It is important when making this effort not to overestimate language abilities and to remember that a much lower skill level of communication is required for "chatting." It is also important to remember that even if a question appears to be more or less understood by the patient, the answer may not be understood by the health care professional well enough to be the basis for a medical decision.

Learning a foreign language to the point of the true bilingualism of a professional interpreter takes a lot of time and practice, and the subtleties involved—and the potentially disastrous consequences of an error in interpretation—are even more telling in the medical context. Proper medical interpretation requires a firm grasp of two different and complex languages to achieve immediate, highly functional, and accurate translation, often at times of high stress and in critical circumstances, plus an ability to communicate effectively in each language at many different educational levels. A modest course of study in Spanish is not enough to interpret reliably in a medical situation. An inexperienced Spanish speaker usually does not know the right Spanish word or may know the right word but not how to pronounce it properly. The results can be confusing, insulting, or comic. One physician who was trying to be friendly with a female patient, asked her, *"¿Cuántos anos tiene usted?"* He intended, *"¿Cuántos años tiene usted?"* ("How old are you?"), but, by mispronouncing the word *años* as *anos*, what he really asked was, "How many anuses do you have?"

In another case, a 70-year-old Cuban woman was being discharged from the hospital into the care of her daughter, also a non-English-speaking resident of Cuba. The woman's granddaughter was doing the interpreting, as she had throughout the hospital stay with reasonable success. The young girl thought she did a good job of clearly explaining the discharge instructions, but her aunt, the person for whom she was interpreting, did not understand that the grandmother's medication was to be tapered off. Instead, after release from the hospital, the aunt cut back the dosage suddenly. This error was discovered only when the patient returned to the hospital very ill with other complications.

The granddaughter, although fully bilingual, was not trained to make certain her aunt fully understood the instructions. In these instances, "back-interpretation" should be used—ask that the interpreted instructions be repeated back so that any miscommunication can be detected and corrected and questions can be cleared up. I am asked many times,

"How do you say this or that in Spanish?" In most cases several words or expressions need to be tried until the interpreter is certain that the patient truly understands what the interpreter is trying to say. Few Spanish-speaking patients or families ask a lot of questions. Most of the time they just nod and go home, wondering what they were told in the hospital or the clinic. Using a professional interpreter who is aware of this tendency helps to avoid misunderstandings.

So goes a typical day in a large university medical center. This account of my daily experiences shows why it is important to always use professional interpreters in medical settings. This may not always be possible, of course, because of limited staffing or in emergencies. It is tempting, when rushed for time, to forge ahead and "make do," relying on dimly remembered high school Spanish plus the patient's or a family member's broken English. However tempting it may be, this choice should be avoided. A little Spanish and broken English typically are inadequate for the level of communication required for good medical care. Using family members, friends of the patient, or Latino cleaning staff rarely is sufficient and can have bizarre consequences.[5,6] Cleaning staff are untrained and inexperienced in medical interpretation, among other problems. Family members—and patients, for that matter—similarly are untrained and inexperienced and may suffer a dramatic decline in English proficiency when confronted with the stresses inherent in the context of illness. It has been observed that the "language of our childhood remains the language used during times of intimacy and stress."[1]

Professional interpreters are the conduit for effective, efficient, and reliable communication between a health care professional and a patient or family member not fluent in English. Health care professionals must recognize that the situation always is bicultural and not merely bilingual. Successful communication between a health care professional and a patient, if a non-English speaker is involved, requires more than mechanical translation between English and the foreign language. The use of a professional interpreter can help achieve this objective.

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- 1.6 million people of Chinese origin live in the US
- Chinese immigrants are heterogeneous in class, occupation, and regional and linguistic backgrounds
- Breast cancer rates for Chinese-American women are higher than for women in China but lower than for white women in the US

Cross-cultural Medicine
A Decade Later

Modesty, Sexuality, and Breast Health in Chinese-American Women

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Although breast cancer rates among Chinese women are lower than among white women, breast cancers and other breast diseases often go undetected and untreated in Chinese women. Cultural values with respect to modesty and sexuality, especially in unmarried women, partly account for a Chinese lack of attention to breast health. In addition, institutional barriers, such as an unavailability of information in Chinese languages, few female physicians, and an absence of educational campaigns, contribute to Chinese women's neglect of breast health.

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One rainy evening in 1977, I accompanied an old friend (and fellow health professional) on a special errand to a Buddhist shrine in San Francisco's Chinatown. We were to pay respects to the burial tablet of her aunt who had recently died of breast cancer. This is the story she told me.

Ah Ling Ee was born in China in 1905 and emigrated to Singapore in her early 20s. In 1956 at age 51, she emigrated with her married sister and her sister's family to the United States. Ah Ling Ee had a sixth-grade education. In Singapore she had worked alongside her sister as a tailor and as a hairdresser. Never having married, she devoted herself to helping her sister raise six daughters. For three to four years, Ah Ling Ee had complained of pain in her hip and lower back *(ill quit tung)*. This is a common complaint among the Chinese, and the family was sympathetic but did not feel the condition warranted a visit to a doctor. In 1972, in terrible pain and thinking she was dying, she asked to be taken to a hospital. A cursory examination showed extensive bleeding from the left breast and the breast obscured and disfigured by a massive growth. The cancer had metastasized to the bone and the liver. Through surgery, chemotherapy, Chinese medicine to keep her strength up, and the daily ministrations of her niece, Ah Ling Ee survived for four years.

As someone who never married, Ah Ling Ee had never had a pelvic examination or a Papanicolaou smear. Neither had she ever had a breast examination. To do so would be an admission that she was a sexual being capable of reproducing. Because she was not married, the idea of sexual activity was not only immodest but repugnant. My friend also told me that her aunt did not want to say anything because the idea of going to a doctor was totally out of the question—she was too modest for that. Because she was single, she also did not want to draw attention to herself. Having her soul tablet placed outside the home was one last expression of her lack of status. Although beloved by the family, she was in death virtually an outsider.

Over the years, my friend gradually expressed her grief at losing someone who was a second mother to her. There was also guilt at being a health professional who could only stand by helplessly as a loved one wasted away in terrible pain. At last, however, there was also anger—anger at the Chinese social and cultural values that prevented her aunt from getting medical attention earlier.

In this article I hope to illuminate the attitudes and cultural and institutional barriers that must be overcome if Chinese women in America are to achieve optimal health. By focusing on the effects of social roles and cultural beliefs on health and illness, I suggest additional areas of questioning for those interested in researching Chinese women's health care needs. In the interests of time and space, most of the examples and discussion focus on breast health care.

Breast Cancer Epidemiology

In all women, including Chinese women, breast cancer is the most commonly diagnosed cancer. Incidence rates seem to increase after menopause,[1] and the death rate from breast cancer appears to increase slightly among women aged 50 years or older.[2]

Chinese women in the United States have a lower incidence of breast cancer (54.0 per 100,000) than white women (86.5 per 100,000),[3] but survival rates at five years are not better for Chinese women (64%) than for white women (71%).[4] A late stage of diagnosis due to cultural and institutional barriers increases cancer mortality. Racially based differences in estrogen metabolism is the prevailing explanation for the disparity that exists between cancer rates of Asian women generally and of white women.[5]

The incidence of breast cancer in Chinese women in the United States is substantially higher than that in Chinese women in Asia,[6] which ranges from 6.1 per 100,000 in Taipei[7] to 18.2 per 100,000 in Singapore[8] and 21.5 per 100,000 in Hong Kong.[9]

Data from Shanghai confirm what had only been suggested previously—that breast cancer rates among Chinese women are increasing steadily. Factors thought to increase the cancer risk of Chinese women who emigrate to the United States and American-born Chinese women include the westernization of the diet (less fiber, more fat), earlier age of menarche, later age of having a first child, fewer number of children, and fewer women breast-feeding.[10]

Breast Cancer Prevention

Breast cancer prevention is primarily focused on early detection and treatment. With slight variation, since the early 1980s the American Cancer Society's guidelines for asymptomatic women are monthly breast self-examination begin-

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ning at age 20; clinical breast examination by a health professional every three years between 20 and 40 years and yearly at age 40 and older; and mammography with a baseline examination between age 35 and 39, every one to two years between 40 and 49, and yearly at age 50 and older.[11]

In an important work, Carter and co-workers found that no instrument existed to assess women's attitudes about their breasts.[12] Many investigators have hypothesized that such attitudes play an important role in breast self-examination and in delay in seeking breast cancer treatment. Understanding these attitudes would be useful in any efforts to educate women about breast health. Carter and associates used a 9-item breast attitude scale measuring women's feelings of pride, comfort with self-touch and examination, awareness of changes over the monthly cycle, and experience of sexual pleasure.[12] In working with Chinese women (except the very young, American-born), such direct questioning would be viewed as intrusive and impolite.

Some cultural reasons should be examined to understand why breast health is a problem for Chinese women, looking first at the demographics of Chinese immigration to the United States and then at sociocultural beliefs about sexuality and health.

Chinese Immigration to the United States

Despite anti-Chinese sentiments and discriminatory laws such as the Chinese Exclusion Act of 1882 and the National Origins Quota Act of 1924, Chinese have never stopped coming to North America since the first arrived after the American Revolution.[13] Large numbers of Chinese came in the 1840s and 1850s to work as farm workers and on the railroad. In 1965 when Public Law 89236 abolished the National Origins Quota System, a large number of young immigrant families and the spouses and children of old sojourners came to be reunited. In 1975 after the fall of Saigon, ethnic Chinese fled Vietnam, Laos, and Cambodia to swell the population of Chinatowns all across the United States.

More recently, events like the uprising in Tiananmen Square in 1989 have provoked the continued exodus of refugees from mainland China. The prospect of the return of Hong Kong to mainland China in 1997 has stimulated a unique movement of Chinese families from both Taiwan and Hong Kong. Young Chinese, some as young as 12 years, are being sent to study in the United States and to establish their families' residency rights.

The Chinese comprise the largest Asian population in the United States, with a total of 1,645,472 persons. The largest concentrations are in the states of California (704,850), New York (284,144), Hawaii (68,804), Texas (63,233), New Jersey (59,084), Massachusetts (53,792) Illinois (49,936), Washington (33,962), and Maryland (30,868). In California the largest communities are in Los Angeles County (245,033) and the City and County of San Francisco (127,140).[14]

Gould-Martin and Ngin categorize four major types of Chinese-American households[15]: the single sojourner, the old immigrant couple, the new immigrant family, and the acculturated suburban family. They conclude that although the first three household types require special attention from health care professionals because of poverty, their language problems, and their residence in Chinatowns, the acculturated suburban family merits special concern only in the area of race and disease epidemiology.

In the past decade, increased immigration and economic and educational diversity among Chinese immigrants have made Chinese-American households less homogenous and more difficult to categorize. Well-to-do immigrant families who are bilingual and bicultural are moving into suburban neighborhoods. Combining incomes from members of large extended families is making it possible for immigrant families to move into middle-class, single-family-home neighborhoods.

Cultural beliefs about the body, health and illness, and social norms do not suddenly disappear in immigrants when they move out of Chinatown. Nor are those who are acculturated without "cultural baggage" that may have ramifications on their health or on their ability to obtain health care. Often these cultural themes lie dormant until a person is under stress (being sick or having a sick loved one) or until a situation causes this backdrop to resurge. In addition, the role played by health care institutions in ethnic minority communities in promoting or discouraging health programs is an important consideration.

Social Role of Chinese Women

The subordinate position of women in traditional China and contemporary overseas Chinese societies is well noted. The means for enlisting women in their own subordination is the use of ideology. The cosmologic basis for this elaborate code of subjugation can be found in Chinese beliefs that date back to the first millenium BC. These held that the universe developed from two complementary opposites, "yin" *(ngam)* the female and "yang" *(yeuhng)* the male. The yin represents the dark, cold, wet, passive, weak feminine aspect, and the yang represents the bright, hot, dry, active, strong masculine aspect.

The natural rhythms of day and night and sun and moon corresponded to the balancing roles of male and female. Man represented the "firm nature of heaven" and woman the "yielding" nature of earth.[16(p173)] Originally conceived as equal and complementary, the elements soon developed a hierarchic relationship juxtaposing the yang over the yin. Yin began to manifest all that was evil, negative, and weak. In contrast, yang stood for all that was good, positive, and strong.

Later Confucius and followers incorporated these revised cosmologic beliefs into an elaborate set of rules governing social interaction that became the dominant ideology of China from the second century BC.

Special books elaborating on appropriate behavior for girls and women were written in the first centuries AD for female audiences. The most well known is the *Nu Jie (Precepts for Women)* written by the scholar Pan Chao. She counseled women to be obedient, unassuming, yielding, timid, respectful, reticent, and unselfish. The result of such passivity was a feeling of powerlessness and vulnerability. The accepted formula is that of "thrice obeying" *(sam sing)*, that as a young girl she must answer to her father, as a wife she answers to her husband, and as a mother she answers to her son. The Chinese patriarchal system considers unmarried women outsiders because they will marry and join their husbands' family line. Females who die before they marry, either in childhood or because they remained unmarried as adults, present an awkward situation because there is no provision for them among the family ancestors. Special "soul

houses" are set up to keep the memorial tablets of such female Chinese.[17]

In overseas Chinese communities all over the world, the Confucian classics hold a revered place in Chinese primary and secondary education. For the illiterate, quotations from these texts are repeated by the educated, and concepts of male superiority and strength and of female inferiority and weakness have been embodied in folklore and permeate overseas Chinese society. Many overseas Chinese women have internalized these negative attitudes, and they are usually not conscious of or able to articulate the ideology that is responsible for their predicament. Like a self-fulfilling prophecy, these ideas have serious repercussions for women's health and well-being.

Cultural Beliefs About Health and Cancer

Among the Chinese, cancer is a relatively new disease. The word for cancer in Cantonese is *nham*, which loosely translated means "growth." Breast cancer is called *yee nham*. There is no mention of this disease in the texts on Chinese medicine.

Most practitioners of Chinese traditional medicine (from the literate tradition) or folk medicine say there are no Chinese cures for cancer. There are ample prescriptions, however, to keep the body well nourished during the often debilitating treatment. This type of prescription is called *boh* or *boh bun* and has been well described in many works on Chinese medicine.

A 1981 project on cancer education for Chinese Americans provides some indication of cancer beliefs (B. Mo, "Chinese-American Cancer Education Project Report," National Cancer Institute, 1981). A total of 62 persons, 28 men and 34 women ages 20 to 67 whose primary language was Cantonese, participated in eight focus groups. All participants were born overseas; 46 were from China, 6 from Hong Kong, 5 from Vietnam, 4 from Burma, and 1 came from Indonesia. Half of the participants had been in the United States less than a year. Their average educational level was the 12th grade, which appears to be higher than that of the usual immigrant. They had much general knowledge about cancer, not all of it accurate. Cancer, they thought, could remain undetected in the body forever, and the following could cause cancer: breathing polluted air (coal dust in their homeland), smoking and drinking, using aluminum and lead utensils, and having certain chemicals sprayed on crops. The relationship between diet and cancer was repeatedly stressed. Frozen foods, preserved foods in cans that contain harmful chemicals, instant noodles, raw foods, and foods preserved in the Chinese manner, such as "salted fish," were to be avoided because they cause cancer. Poor or inadequate nutrition was thought to make people susceptible to cancer.

Only 6 of the 62 thought it was important to have regular medical checkups. Only 6 (18%) of the 34 women went for yearly pelvic examinations. This reluctance to seek the care of a physician should not be interpreted as a rejection of preventive care. In fact, there is ample evidence that Chinese are attuned to some preventive strategies such as exercise, diet, and postnatal care.[18] The reluctance to seek care from a physician stems from the inconvenience of having to make and keep appointments and the high cost. In Asia physicians prescribe and dispense medication. There is usually no charge or only a nominal fee for physicians' services, the real cost of the visit being the charge for the medicine. Consequently, the idea of a visit for a checkup without medication does not fit Chinese patients' expectations. This feeling of incompleteness may progress into a lack of confidence in the physician. In my own research, English-educated, foreign-born Chinese have said to me after a visit where medication was not prescribed, "Isn't it strange, we weren't given a prescription. Perhaps we should consult someone else."

Sexuality, Power, and Health

In several of the essays in Wolf and Witke's book, evidence exists for a Chinese conception of women as "weak, timid, and sexually exploitable as well as dangerous, powerful, and sexually insatiable."[18(p2)]

Women's power lies in their contribution to the formation of the fetus and the physical and social danger of contact with birth and menstrual fluids. In women's fertility lies the fate of the patrilineal group. Women are viewed as dangerous socially because their influence over descendants of the family can have repercussions for its survival as a unit.[19]

According to Wolf and Witke, "gestation and childbirth, sources of great good as well as immense unacknowledged female power, have acquired over the centuries an enormous ritual burden of negative sentiment,"[18(p3)] which has had a debilitating effect on Chinese women today.

Ham suup, a Cantonese term that means "salty and wet," is the colloquial term for sexuality. Most frequently used in a derogatory manner, the words describe anyone who is sexually inappropriate. Being overly concerned with another person or talking about or touching one's body is classified as *ham suup*. Expressing curiosity or being knowledgeable about the body is also *ham suup*. Consequently, sex education is not considered an appropriate topic for polite conversation.

In many cases sex education is really birth control information, which is deemed appropriate only just before marriage. To obtain birth control information today usually involves a physician visit, which may also be the first time a Chinese woman receives a complete physical examination with a pelvic examination, a Papanicolaou test, and a clinical breast examination.

Discussions of Chinese women and health invariably mention modesty as the reason women are reluctant to be examined by male physicians. Cultural beliefs continue to be a barrier to health care. Pillsbury notes that in Taiwan, men are never permitted in a delivery room lest they be polluted—made "dirty"—by the blood emitted by women.[20] In China about 90% of obstetricians and gynecologists are women because of the traditional female reluctance to have reproductive problems dealt with by men.[20] This high percentage of women in obstetrics and gynecology may well be due to persisting beliefs in the polluting effects on men of menstruating blood.[15]

Knowledge of Chinese women's attitude toward sexual experiences is limited, but women tend to be "negative and heavily influenced by a fear of the exploitation of their sexuality." Chinese women feel vulnerable not only to illness and natural harm but to exploitation by other people.

Further, according to Ahern,

> during intercourse a man absorbs the female yin essence, which strengthens his vital powers. Ejaculation, however, results in the debilitating loss of vital yang essence. Too frequent intercourse so drains a man's vital essence that he is vulnerable to several serious diseases. For this reason numerous techniques are recommended that enable men to avoid ejaculation; women are in no danger, for their supply of yin essence is inexhaustible.[19(p209)]

Feuerwerker in a discussion of Chinese women's potential for power says that a popular theme used by women writers is of "a man done in by lust for which a woman is to blame."[21(p147)]

Institutional Barriers

Mammography, particularly screening mammography, is a relatively new procedure. In the United States mammography has become common only in the past decade. The American Cancer Society's Breast Cancer Detection Awareness Program became activated between 1986 and 1988. In Ottawa, the capital of Canada, the first government-sponsored breast screening clinic opened only in late 1991. In a 1977 trip to the Peoples' Republic of China, participants noted that they were shown conventional film mammograms, mammography was not done in most hospitals, and it was not used for screening women for breast cancer.[22,23]

Misinformation about breast cancer and mammography is not just a cultural problem; the lack of breast health education is an institutional problem. Too often groups of people are criticized for their lack of awareness of an issue or a problem when the issue is so new that it has only recently emerged in the English-language media. Defining the problem is critical: often health programs are funded without adequate provisions made for outreach and education because these are seen as nonessential.

As an example, for more than five years, a mobile van offering low-cost screening mammography has been available to communities in San Francisco. The van, staffed by female technicians, is parked near a different shopping area each week. Unfortunately, funds for outreach or education were not available. Women who could read and understand English might have received information about breast cancer and mammography through the news media, and the van's schedule was published in a local newspaper. Women whose primary language was not English, however, would have no information about breast cancer, mammography, or the van's purpose or schedule.

The lack of community response to the van's appearance in San Francisco's Chinatown prompted the planning and implementation of a Breast Health Awareness Day for the community. Although the event was successful, planning for the event did point out several institutional problems.

All the Chinese health professionals who helped plan the event worked outside of Chinatown. Some of those who worked in Chinatown were reluctant to participate because they felt that breast cancer was not a critical health issue for the community and that Chinese women would not attend the program either because they did not perceive breast cancer as a problem or out of modesty. The Chinese medical establishment did endorse the program, however. In addition, a Mandarin-speaking oncologist who was a long-time American Cancer Society volunteer agreed to speak during the lunch break. The necessity of providing clinical breast examination by a licensed physician presented two problems. Although many breast health care practitioners are female nurses, male physicians still outnumber female. Consequently, only one female English-speaking physician was available, and the decision was made to have male physicians perform the clinical breast examinations. In retrospect, female nurses could have been used for the clinical breast examination because the program was doing a screening and not a diagnostic mammogram.

With a planning committee composed of both Chinese and non-Chinese community health professionals and extensive education through the use of the Chinese language media, Breast Health Awareness Day, sponsored jointly by the San Francisco Chinatown Young Women's Christian Association and the local chapter of the American Cancer Society, attracted 109 Chinese women to a screening that previously had engendered no community participation. During the program, 97 (89%) were taught breast self-examination and 91 (84%) received a clinical breast examination. Of the 94 women eligible for mammograms, only 55 (59%) received them because the demand exceeded the capacity of the mobile van.[22]

The importance of screening is demonstrated by the following cases.

Case Examples

Case 1. Sadhi, a 32-year-old single woman from Hong Kong, came here to join her fiance, a 35-year-old electrical engineer also from Hong Kong. They had been introduced through mutual friends. She came to our attention because she needed a premarital examination and wanted information about birth control before her impending marriage.

Sadhi informed us that this was her first pelvic examination and Pap smear. She also had never heard about breast self-examination and felt embarrassed even to discuss it. She told us that unmarried women were not supposed to talk about these things. On manual palpation a lump about 1.27 cm (½ in) in diameter was discovered in her left breast. She was sent for an ultrasound examination and aspiration, upon which the lump was diagnosed as a benign cyst.

Case 2. The patient, a 58-year-old wife and mother of four originally from mainland China, had been in the United States six years. She had all of her children in China and could not recall ever having a pelvic examination or a Pap smear, nor had anyone ever examined her breasts. Because she was beyond her childbearing years, she had not felt the need to be concerned about her female parts. Her daughter, a nursing student, brought her to the screening. On manual manipulation a lump was found in her right breast, and she was referred to her health maintenance organization for further evaluation.

These two case histories concern women at the far ends of the reproductive cycle, one at the beginning and the other at the end. Both women think female organs cease to function if they are not used in procreation.

A unique feature of the Breast Health Awareness Day was the outreach to young Chinese women, who were encouraged to talk with and accompany their grandmothers, mothers, and aunts. In immigrant communities, the young are often called on to translate for their older relatives. By drawing on this common practice, the planners hoped to engage and educate several generations of women at once.

The difficulties that these projects had in recruiting female physicians generally and also those who could speak a Chinese language point to the dearth of bilingual, bicultural female physicians in our community. To remedy the situation, institutions of higher learning need to recruit and train more women physicians. In addition, the community must promote the notion of cultural diversity and instill in young people the need to learn and preserve the best of our cultural beliefs, practices, and languages.

Conclusions

Community organizing, outreach, and education are essential if Chinese-American women are to achieve optimal health and obtain necessary health screening and treatment. Health professionals, even those who are Chinese, often make light of the tenacity of cultural beliefs and social constraints. By understanding the social and cultural context of beliefs about health, sexuality, and fertility, health professionals can provide more sensitive health care to Chinese-American women. Information about specific health practices and their traditional rationale can help support those that have a positive effect on health. Only by understanding such cultural ideas in detail can we as a society sensitively discourage practices that are harmful.

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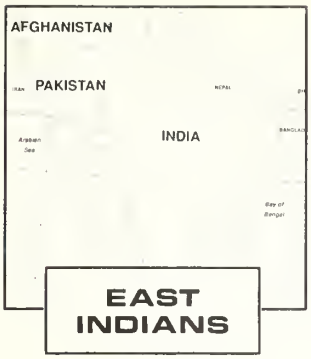
Cross-cultural Medicine
A Decade Later

- 815,000 migrants from India live in the US, mostly (35%) in the East
- Migration began around 1900, but most migrants arrived after 1965
- Although East Indian migrants come from several different ethnic groups and backgrounds, the Ayurvedic tradition of medicine is a common thread



Health, Illness, and Immigration
East Indians in the United States

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East Indian immigrants to the United States represent the diversity in religion, language, and culture that exists in India, so it is difficult to make unequivocal statements about their health beliefs and behaviors. Despite the diversity, an understanding of *Ayurvedic* humoral concepts of health and illness provides a key to some pervasive and persistent ideas and practices. India has a pluralistic medical system in which Western medicine, which is increasingly popular for some ailments, is one option among many. Even those who are familiar with the "Western" medical system in India may find American medicine alien.

(Ramakrishna J, Weiss MG: Health, illness, and immigration—East Indians in the United States, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:265-270)

The East Indian presence in the United States is about a century old. Other than occasional immigrants, the first groups of Indians, mainly Sikhs from the northern Indian state of Punjab, arrived at the turn of the century.[1] Since the 1960s immigration has increased, primarily through sponsorship.

Some of the differences in the health and illness behavior of East Indians arise from their particular beliefs and practices; other differences are the result of features common to all immigrant communities. The latter will be mentioned only in passing but deserve consideration because they influence health and illness behavior.

In this article we briefly consider the diversity in the East Indian community, identify vulnerable groups within the immigrant population, and highlight aspects of a traditional Indian medical system that affects health behavior. In the last section we discuss possible conflicts that may arise in clinical situations because of differing perspectives, values, and beliefs. Some of the generalizations and examples are derived from fieldwork one of us (J.R.) did among the Sikh farmers of Yuba City in northern California and from the other's (M.G.W.) experience in cross-cultural medicine in India and the United States.

East Indians in the United States

East Indians do not constitute a cohesive community in most parts of the United States. There are notable exceptions, however, such as the Sikh farmers of Yuba City[2-4] and the Gujaratis of San Francisco.[5] Most large cities have sizable East Indian populations of diverse linguistic and ethnic origins. Many East Indians are well educated and work in well-paying professions and businesses.

Diversity of East Indian Immigrants

As with Indians in India, it is difficult to make a statement about the East Indians in the United States without finding exceptions to the generalization. For instance, most people assume that all Indians, or at least all Hindus, are vegetarians. This is not true. Many Indians eat some meat but usually not beef; meat is not the main part of their diet. Even in those families in which meat is not prepared at home, some members, especially men, will occasionally eat meat outside the home.

India is not a monolithic society; diversity is the rule. There are 16 recognized languages in the constitution, and many others are spoken, including numerous tribal languages without written scripts. Although most of the people are Hindu (about 83%) and the Hindu ethos pervades, there are substantial numbers of Muslims (11%), Christians (2%), Sikhs (2%), Buddhists, Jains, and others. In fact, India has the second largest Muslim population of any country.

In addition to these differences, diversity among East Indian immigrants stems from several other important factors:

- *Education.* Immigrants range from barely literate peasants to highly educated scientists and professionals. Within families, too, there may be considerable variation in educational background.
- *Income.* There is much variation in income, ranging from poor, new immigrants to well-established, successful professional or business persons. Some less-educated Indians have found occupational niches in motel management and orchard farming.
- *Acculturation.* Familiarity with the English language

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and with American customs ranges widely—from new immigrants from rural India who speak little English, to second-generation descendants, to "Americans" with little knowledge of India and its traditions. Interaction with the larger society also differs. In rural areas, East Indian migrants might interact mainly with other East Indians, whereas professionals in cities may have little contact with other Indians. In most cases ethnic networks ease the new immigrants' transitions[6] and provide social support.

• *Reasons for immigrating.* Some people come to the United States because of opportunities to better themselves, and some come because their providers have immigrated. Migrants maintain close contacts with kin in India and may even see immigration as a temporary adventure. Other East Indians, especially those from East Africa and Fiji who have emigrated for political reasons, have little hope of returning to these countries. Also, they often have few remaining or immediate ties with India.

Vulnerable Groups

The US immigration law ensures that capable, self-reliant, and successful people immigrate to the United States. These people, however, sponsor their dependents who may be less able to prosper in this country. All have a rosy picture of the United States, and some are ill prepared for the hard work, especially the loss of status associated with service jobs. They miss the warmth of their families. Unlike professional occupations, labor-intensive businesses such as orchard farming or motel management can accommodate unskilled relatives who, once they learn the business, can branch out on their own.

Apart from the stresses and strains that all new immigrants face, immigrants who are economically or otherwise dependent are especially vulnerable because they are without traditional support networks. Two distinct subgroups of dependents are spouses and parents.

Spouses. Arranged marriages are still the norm in India. This practice continues even among some immigrants. Although an effort is made to marry within the same caste group, immigrants, who have a higher status by virtue of residence in the United States, can aspire to marry into a higher social stratum. For instance, in Yuba City an agricultural laborer might marry an urban postgraduate woman from India. She might agree to the match because the groom is in the United States, not realizing that he lives in a rural area and works on a farm. Matters are worse for her because she becomes cut off from her accustomed family support network. Similarly, an Indian engineer may marry an East Indian woman and immigrate to this country, only to find that his qualifications are not recognized and he is forced into a "demeaning" blue-collar job. The fact that traditionally the man is supposed to play the dominant role, that is, provide for and support the wife and family, increases the stress of immigration. These situations are less likely to occur in traditionally arranged marriages where liaisons are made within the same social group and the risk of conflicts arising because of differences in life-styles and expectations is minimized.

Older adults. Many older East Indians live in the United States only because their children live here. They, too, are cut off from their social support networks—their friends and relatives—and from religious activities that form a vital part of their lives. In India they would be respected for their wisdom, but in the United States, in an alien culture, they are no longer effective advisers to their families. Not knowing the language or customs of US society reduces the degree to which older Indians can guide younger family members.

Many older Indians play major roles in providing antenatal and postnatal care. Frequently female relatives travel to America specifically to assist new mothers and may reinforce traditional beliefs and customs. For instance, it is widely believed in India that colostrum is unsuited to infants. Most women think that the milk does not "descend to the breast" until their ritual bath on the third day, so newborns are fed sugar water or milk expressed from a lactating woman. Older relatives often share responsibility for child care. Conflicts can arise when their traditional ideas of child rearing and caring differ from those of the parents. These roles played by older Indians have another implication: They should be included in discussions of therapy for children and when discussing antenatal and postnatal care.

Intergenerational conflicts. Intergenerational conflicts are exacerbated in families where India-born parents retain traditional ideas and values, while their children born and brought up in the United States think and act like Americans. East Indian parents are ambivalent toward American culture: They would like their children to become American enough to succeed, but they are apprehensive the children will lose Indian values. One way of having the best of both worlds is to lead an active American public life and an essentially Indian domestic life. Many Indians in India are accustomed to compartmentalizing their lives in this way, but East Indian children in the United States may feel torn between the two cultures. Many parents fear the increasing violence and the influence of drugs in schools, so some send their children to India for schooling. When their children are older, they may arrange marriages with Indians in a bid to retain "Indianness," thus laying the groundwork for possible familial and marital conflict (A. Fernandes, "U.S. Indians' Marriages Are Now Breaking Up More Often," *The Times of India,* February 11, 1992, p 4).

The Traditional Common Ground

Despite these differences, a common thread runs through the Indian view of health and illness. Health-related behaviors are learned through early childhood socialization and derive from the traditional *Ayurvedic* (*ayur* = "longevity," *veda* = "science") principles. This forms a codified "great tradition" of medicine in Indian society, in contrast to the "little traditions" of medicine (folk medicine) that reflect local adaptations and include features that originate from specific regional cultures.[7] In addition, in India the process of social change leads "lower" castes to emulate "higher" castes by adopting their customs (such as becoming vegetarian) and even reworking the history and origin of their caste. The Indian anthropologist, Srinivas, calls this the process of "sanskritization,"[8] referring to the status of the classical Indian language, Sanskrit. Simultaneously, higher castes undergo a process of "westernization" as they seek to emulate Americans and Europeans. Remarkably compatible with such aspirations to enhance social status, "pan-Indian" Ayurvedic ideas greatly influence Indian thinking about health.

Fundamental Concepts of Ayurveda

The term "ayurveda" indicates a positive attitude toward health. An interrelationship between the universe and the

body is a fundamental principle of Ayurveda. The universe contains five elements (*pancabhuta*): water, fire, earth, wind, and ether. Three of these universal elements, *tridosa*, have analogues in the body as humors: fire (as bile), water (as phlegm), and wind (as wind).[9] When a delicate balance of these humors is achieved, a person is healthy, whereas a disturbance of this homeostatic condition causes illness.

Although blood is not mentioned in most classical texts on Ayurveda, it plays a crucial role in the maintenance of health in the Ayurvedic system of medicine. The fundamental importance of blood to health is reflected in the Ayurvedic notion that "the strength or weakness of *dhatu* (elements) depends upon the richness or poverty of blood."[10(p46)]

In Ayurveda various causes are held to vitiate the humors and, in turn, weaken the elements of the body and cause illness. Consuming certain foods that aggravate a particular humor is one of the main causes of a loss of humoral equilibrium.[11] Certain foods, such as chicken, garlic, and cloves, are considered "hot" because they increase the "heat" in the body. This has little to do with the actual taste or temperature of the food or the body. Similarly, other foods, such as yogurt, oranges, and rice, are "cold" because they make the body "cold." The nature of a given food can be changed by spicing or cooking: for example, the addition of garlic or roasting will make a food hot, while soaking it in water or mixing it with yogurt will make it cooler.

A person is healthy when the humors (wind, bile, and phlegm and the balance of hot and cold) are in equilibrium and ill when the humors are out of balance. Because the temperament or constitution of each person is unique, the exact nature of this humoral balance differs from person to person. What is an excessive humor in one person may mark a normal humoral distribution in another.

To be healthy it is necessary to have a good digestive system because it is here that the crucial transformation of food into humors and body constituents occurs. Undigested food is useless and, indeed, harmful. Ingested food is "cooked" by the digestive fires and converted into food juices and wastes. The food juices, by successive transformations, become flesh, bone, marrow, blood, and semen. These are the constituents of the body.[9] During the process of digestion, the three humors are also released into the body or into wastes. An excess or a lack of waste products results in disequilibrium, which then causes illness.

In Ayurvedic theory the key to health is an orderly daily life (*dinacharya*) in which personal hygiene, diet, work, and sleep and rest patterns are regulated. A daily routine has to be established for each person, depending on his or her constitution, and changed according to the season (*ritucharya*). Therefore, women have to be vigilant about their children's diets and the effect of particular foods on children's body constitutions. Adults have to determine carefully which habits are best suited to their health.

Ayurveda distinguishes between health in general, or ordinary health (*samanya swastham*), and ideal or ultimate health (*parameh swastham*). Although there is a distinct concept of mind and body in Ayurvedic thought, the Ayurvedic concept of health and illness is a psychosomatic one[12]; the prefix "psycho," according to the Hindu concept of health, also encompasses a spiritual aspect. Mind, body, and soul are interconnected components of a system in which malfunctioning in one component, or an upset in the relationship between the components, disturbs the harmony of the whole system. This disequilibrium causes sickness.

The Ayurvedic view of health emphasizes social, environmental, and spiritual contexts, and the key concept is harmony within the organism and within the system of which the organism is a part—that is, society at one level and the universe at a higher level. All components of health are seen as interdependent and interrelated; a change in any one component will result in an imbalance in the other components. The notion of health in Ayurvedic teachings is dynamic and involves process. Ultimately, according to Ayurvedic theory, the body and the cosmos are reflections of each other.[12]

Traditional Influences on Perceptions of Health and Illness

These Ayurvedic concepts help to explain why many East Indians are greatly concerned about everything they ingest. They place importance not only on the nutritional value of the food but also on its inherent nature—whether it is hot or cold. They are also preoccupied with the timely elimination of waste matter. Because blood is seen as the life force, created through successive transformations of food, it is perceived as precious and not something to be wasted. Hence, there is a reluctance toward the drawing and donating of blood. Because semen is the last product in the food transformations, it is more precious still. Young men may be especially anxious about a loss of semen.[13]

Although Ayurveda is the dominant tradition, there are regional variations, such as Siddha, which is more common in South India, and Unani-Tibb, which is the Arab-influenced system of medicine prevalent in the North and in other areas where there is an Islamic influence. In addition, there are local bonesetters, snake-bite curers, faith healers, and shamans. Practitioners of these systems vary in their technical knowledge and professionalism. Unlike the formal, text-based medical systems, much of the local knowledge—common medical perceptions and beliefs—is not codified or standardized[14]; therefore, great regional and idiosyncratic variations exist. This reflects the inclusive, eclectic nature of Indian culture: it readily adopts, adapts, modifies, and makes foreign elements its own.[15] Thus, German homeopathy is considered by most Indians, including some homeopathists, to be a traditional Indian medical system. This is the context of medical practice in India.

Use of Western Medicine in India

There has been considerable change, particularly in cities, since the early 1950s when Carstairs[16] and Marriot[17] wrote of the resistance of the India villager to Western medicine. "Allopathic" medicines are now readily accepted for most acute conditions. In fact, allopathy (as mainstream Western medicine is known in India) is the preferred type of care in most places where it is accessible. Resistance to or a reluctance to use Western medicine, however, cannot be ignored: Other systems of medicine are still used in India and are preferred for certain problems, including some forms of mental illness[18,19] and many chronic illnesses. In such a pluralistic medical system, allopathy (biomedicine) is just one of many kinds of medical care available.

The home management of health and illness continues. Particular attention is paid to diet, exercise, rest, and exposure to the elements, in conjunction with treatments from different medical systems. For instance, patients attending

allopathic clinics often inquire whether they should take their medication(s) with hot or cold water and whether they should include or exclude certain foods in their diets. Most successful allopathic practitioners give instructions to their patients regarding diet. A patient suffering from a cold and sore throat will be encouraged to refrain from eating cold foods, such as oranges, guavas, and grapes, and from taking cold drinks or ice cream. Among hot beverages, "hot" coffee is preferred over "cool" tea, even by many educated South Indians. Ayurvedic humoral concepts also apply to mental illness.[20,21] An elderly Sikh who had lived in America for many decades was convinced his relative's mental illness was due to excess heat resulting from an overconsumption of garlic.

Even though Indian allopathic physicians diagnose and treat ailments in accordance with Western concepts, the practice and organization of allopathic medicine are essentially Indian.[22] Some features of allopathic and Ayurvedic or other traditional hospitals in India have more in common than do allopathic Indian and American hospitals. In India, family involvement in patient care is not only recognized but expected. The family looks after the patient's needs and provides all but expert medical care. This provides vital psychological support to the patient. Visiting hours exist but are seldom adhered to; relatives may be required to stay overnight to give food and care.

Potential Conflicts

Language

Although most Indians in the United States understand some English and many are fluent, there may be considerable difference in English usage. It is often said that the English and the Americans are divided by a common language. An even deeper division exists between Americans and East Indians because the latter essentially speak Indian English with an English vocabulary. Many expressions regarding health are not easily understood by the average American. For instance, someone who is moody may be described as "his moods are off."

Besides differences in English vocabulary, a more basic problem may exist. Many expressions to describe feelings such as pain and distress are learned in early childhood in the mother tongue.[23] East Indian patients, however facile in English, may never learn the English vocabulary to express these feelings.

In addition to the misunderstandings because of differences in language, problems may arise out of patients' eagerness to please and to say "yes" even when they do not understand. This is more likely when the status differential between physician and patient is great. Even in present-day India, white people are held in high esteem. The pattern of communication between whites and Indians is determined by the feeling that Indians cannot contradict or disagree with white people of high stature.

Nonverbal communication presents problems as well. East Indian patients may not know how to respond to the American physicians' social smiles. In India smiles are only exchanged between social equals and in informal situations. In turn, an American physician may mistake the meaning of a lateral movement of the head. Instead of nodding, East Indians use head shaking to denote "yes" or to make a positive assertion. Women, who tend to be less vocal, may use these gestures to indicate their interest and response.

Those who do not understand English must speak to health professionals through an interpreter. This modified communication is fraught with hazards because a speaker's nuances and subtleties are rarely translated. In fact, interpreters may choose to edit, sanitize, or present information in a manner most acceptable to Americans. Except in areas where there are a large number of East Indians who speak the same language, such as in Yuba City, there are few, if any, official East Indian interpreters.

Social Relationships

Even in Yuba City where the health staff are well-known members of the East Indian community, patients do not want to reveal their problems.[3] Sometimes educated young members of a family are asked to translate. This can lead to complications because of role reversal: Older family members are put into subordinate roles, and youngsters may be inhibited about telling them what to do.*

This brings us to the curious paradox of confidentiality and privacy. Most East Indians seek to protect their family secrets from the rest of the East Indian community, but privacy and confidentiality within the primary group, the family, are not highly respected, especially between spouses and siblings. Women shy away from discussing sexual activity and contraceptives in the presence of men, even their own partners. Sex education is uncommon. People may not understand the terms for genital organs and sexual functioning.

Although women in India routinely consult physicians, few undergo thorough examinations. Even those who have borne children may never have had a pelvic examination. A full explanation and much reassurance are essential before a pelvic examination. Most women prefer and expect all obstetricians and gynecologists to be women.

Somatization is common.[24] Psychological distress may be expressed in this way, particularly by women.[25] New immigrants may complain of headaches, a burning sensation in the soles of the feet, and tingling pain in the lower extremities.

East Indian patients, particularly women and youngsters, will not visit a physician unaccompanied. The accompanying person expects to participate in giving the patient's history, to act as a chaperon during the physical examination, and to be actively involved in making decisions about therapeutic strategies. This may pose a dilemma for American clinicians whose training emphasizes autonomy and privacy. Mental health professionals, especially, may find it difficult and problematic to separate patient and family too early in an initial consultation.

Expectations

Expectations of a "good" physician's demeanor and behavior vary. Some East Indians think that a detailed physical examination and the gathering of a complete history are hallmarks of a good physician. Others resent in-depth inquiries about past events that they may think are irrelevant. For many Indians, time sense is elastic. Exact times, dates, and frequencies do not have the same meaning as they do for Americans. Indian patients may eagerly recount their diets, relate symptoms to changes in weather conditions, and provide other information that American physicians may consider unnecessary. Still others may swear by physicians who do not do physical examinations but prescribe simply by looking at

*See L. Haffner, "Translation Is Not Enough—Interpreting in a Medical Setting," on pages 255-259 of this issue.

the patient or by feeling a pulse—as Ayurvedic practitioners do routinely.

To some extent expectations vary according to the status of the patient. In India, patients of high status are treated as social equals and in a socially intimate manner that American physicians may consider unprofessional. Such patients expect preferential treatment—no waiting, detailed explanations, and convenient appointments. Poorer, low-status patients are accustomed to the opposite—curt behavior, social distance, long waiting periods, and little explanation.

Several Yuba City Sikhs complained of having to wait for the results of expensive diagnostic tests before their physicians treated them.[3] In India, they recollected, physicians treated patients largely on the basis of a physical examination and clinical history. This attitude may be changing as "high-tech" diagnostic laboratories proliferate in all Indian cities. Now Indian patients may feel cheated if they do not undergo tests. Some even request computed tomographic scans and electrocardiograms. Yet, most patients do not understand the need for or the nature of these tests and their use in diagnosis; many think of them as a part of therapy.

Multidrug therapy is common in India. Patients routinely receive three or four medications in addition to injections. Medication potency may be judged by its reputation and appearance. Capsules are thought to be stronger than tablets. The color of the tablets may be associated with their effects; most patients are disdainful of plain white tablets. In South India, for instance, dark-colored tablets are thought to be heating.[26] Even Ayurvedic medicine no longer comes in dull, dark-colored powders or pastes but is colorfully packaged in capsules. In addition, brightly colored vitamins, fizzy calcium pills, or vitamin B_{12} injections are prescribed. Patients do not *have* to consult a physician for medications; medicines, including most prescription drugs, are readily available over the counter, or the pharmacists are ready to prescribe them.[27,28] Medicines alone do not cure; a physician's skill and attributes matter. This "hand quality" of physicians is highly regarded: Patients often request physicians to personally hand them their medicines.

Expectations and values are not determined solely by tradition. Injections, which represent powerful interventions, are immensely popular. It is widely believed that most illnesses cannot be cured without resorting to injections[29]; hence, patients or caring family members request them. There are several explanations for this belief: Injections have rapid action and afford prompt relief; the first antibiotics were given in injection form; and because the drug is not ingested, it may not disturb the "system" as much. Physicians have encouraged this attitude toward injections because compliance is enhanced and fees increase with each patient visit. Although injections are not a part of any of the traditional Indian health systems, this method of administering medication has been widely adopted. A study in South India reported that as many as 50% of patients visiting Ayurvedic practitioners received injections[30]; another study in India showed that 86% of traditional healers administered injections.[31]

Because most Indians are concerned about the effects of whatever they ingest, they carefully monitor changes after starting any new medication to determine whether it suits their constitution.[32] Any alteration in their body functioning is attributed to the side effects of the medication. Action is taken to counteract adverse consequences; modifying the diet is the first option. If this does not work and the patient or the family thinks that the side effects are even more troublesome than the illness, the patient may stop taking the medication. This may be a problem toward the end of a regimen when patients think they have recovered.[33]

Some Indians think that Western medicines provide only symptomatic relief but do not attack the root cause of disease. Some patients think that physicians prescribe more medicine than necessary, so they save it or give it away. Hence, it is important for physicians to emphasize the need to finish a course of medication to ensure a complete cure.

Access to Care

In India the public health system is run by the state governments, and theoretically all have easy access to it. There is a strong private medical system that operates on a fee-for-service basis. Families, especially the poor, spend a high proportion of their income on medical care. In such families the male breadwinner and sons may have priority for treatment over women, girls, and elders.

Medical insurance does not exist on a wide scale, although many jobs provide medical coverage as a fringe benefit. Workers do not contribute toward this. Only recently have some insurance companies begun to popularize medical insurance. Therefore, recent East Indian immigrants to the United States may not understand the concept of health insurance and resent having to allocate a substantial portion of their meager resources to the eventuality that they might get sick and require medical care. Many also get only the basic coverage and face economic hardship if they require admission to hospital or surgical treatment.

The legal aspects of medicine in India are largely confined to medicolegal cases. Malpractice is not recognized as a breach of legal contract. On the whole, Indian patients tend to be subservient and do not openly question physicians' behavior or treatment; if they do not like a particular situation, they just change physicians. Consequently, patients who appear to be quietly compliant may simply not return to a particular practitioner. Others may be indignant about the extensive tests that most physicians use to confirm diagnoses and monitor treatment.

Indian physicians tend to be directive and give little explanation about the cause of an illness or the course of treatment. Most East Indian patients in the United States appreciate the information that physicians give, but some consider it excessive. The attitude of accompanying persons depends on their social status and role in the family—how responsible they are for a person's welfare. Again, most patients and chaperons like being involved in decision making, but a few may prefer physicians to just tell them what to do.

Families are especially protective of an ill member; they do not want to disclose the seriousness of an illness to the patient or speak about impending disability or death for two reasons: Speaking of possibilities may render them too real, and a traditional Indian does not speak lightly of death; and many people think that if a patient knows the gravity of the illness, he or she will give up hope and die. This conflict between medical ethics and patients' values may present a dilemma to physicians. There are no easy answers to these potentially difficult situations or conflicting values, but as research in Yuba City showed,[3] if medical interventions are perceived to be efficacious, people accept them. For example, women who traditionally gave birth at home and strictly

followed the associated rituals found some aspects of giving birth at a hospital traumatic—being isolated from female kin, having to drink "cold" orange juice, and having to walk soon after birth. Nevertheless, they readily acknowledged that there had been deaths at childbirth at home, and therefore in-hospital medical care is good.

As medical care in India becomes more sophisticated, biomedical diagnostic and treatment measures will hold no surprises for East Indian patients. The organization of medical practice, however, will remain sufficiently different that a special effort will be required on the part of patients and health professionals to ensure appropriate and satisfactory health care for East Indian immigrants in the United States.

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Cross-cultural Medicine
A Decade Later

- Worldwide, in 1990 Afghans were the largest refugee population, with over 6 million people displaced
- Migration has been triggered by 10 years of fighting between pro-Communist forces and *mujahideen* (Freedom Fighters)
- Total Afghan population in US is estimated to be at least 100,000

Health Issues of Afghan Refugees in California

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Since the 1979 Soviet invasion of Afghanistan, more than 6 million Afghan refugees have become the world's largest refugee population. Although refugees in Pakistan and Iran are now beginning to repatriate, continuing political turmoil in Afghanistan and children's acculturation and educational opportunities will keep many Afghans in the United States permanently. Although there are no accurate statistics, local resettlement agencies and Afghan community leaders estimate that there are 10,000 to 35,000 Afghans in northern California. They suffer from a variety of problems common to refugees: language, economic and occupational problems, and substantial challenges in psychological, family, social, and cultural adjustment to the United States. Although many Afghans are doing well, many others have depression, psychosomatic symptoms, and posttraumatic stress disorder.

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Migration and subsequent adjustment cause stress, which increases the risk of sickness.[1,2] Stress may be greater in refugees who leave in fear for their lives and have had traumatic escapes. Uprooting is often associated with mental disorders because it disrupts the continuity of a person's self-concept and interrupts meaningful relationships with surroundings.[3] Depression and stress-related symptoms are prevalent. Afghan refugees have had many losses: Relatives were killed or left behind, and the refugees lost their status, language and vocational competencies, and their country, for which they mourn.

The primary problems of one Afghan physician's patients, 75% of whom are Afghan, are depression and psychosomatic illness; their major complaints are headaches and musculoskeletal problems, such as joint and back pain.[4] A 37-year-old woman described her experience as follows:

> From the day I come to this country, I feel terrible pain in my back and right arm. I went to so many doctors. They took x-rays but every time, they told me that everything is OK. I'm so confused. I ask myself, "what kind of doctors are they that they don't know my problem?"

In this article we focus on Afghan refugees in California, basing our discussion on ethnographic research and clinical work with Afghans. Since 1985, we have worked with Afghans in several capacities: consulted with health providers, served as cultural interpreters and advocates, and provided information and health education to Afghans through the Mid-East Study of Immigration, Health, and Adjustment (S.I.H.A. Project), a health resource center for Middle Eastern immigrants in the School of Nursing, University of California, San Francisco.

The ethnographic research on which this article is based includes an interview study from 1985 to 1988 in which 28 Afghans reported 70 ongoing symptoms; psychosomatic indications of stress, elicited by the Health Opinion Survey, were significantly higher than among Latino and Iranian immigrants.[4] Since 1990, one of us (J.G.L.) has focused on health and adjustment issues and access to care; 20 health and social service providers were interviewed, and two research assistants interviewed 62 Afghans in Dari or Pashto. One of us (P.A.O.) did dissertation research on family intergenerational conflict and the adjustment of the elders, for which 60 Afghans from three generations were interviewed.

Afghan Culture

Traditional customs in Afghanistan include arranged marriages, ideally between first cousins, polygyny when affordable (as many as four wives), and a strongly patriarchal family system. Women are less educated than men, do not work outside the home, and interact almost exclusively with female relatives. The most important social unit is the extended family, which averages 50 to 75 people, contained within a tribal unit of 1,000 or more.

Most Afghans are staunch Muslims, with the majority following the Sunni branch. Muslims pray directly to God privately or in a mosque or *jumat* (congregation). They must act in accordance with God's commands as described in the *Qur'an* (Koran); these include rules of cleanliness, diet (avoidance of pork and alcohol), and prayer (five times a day, facing *Kaba*, Mecca).

Although there are 19 ethnic groups in Afghanistan,[5]

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most Afghans in the United States are Pushtun and Tajik. The two major languages are Dari (Afghan Farsi) and Pashto. The Afghan population is heterogeneous and divided based on ethnicity, politics, social class, and urban or rural origin. The first Afghans to arrive in California (1980) were the urban, formerly wealthy, and highly educated elite. They were followed by their middle-class relatives who were less educated, with some illiterate in their own language.[6]

Afghan culture in the United States is not homogeneous and is in transition. Families range from traditional to cosmopolitan, depending largely on urban and educational background and personal preference. For example, one traditional family eats only specially butchered meat, maintains strict prayer rituals, and wears traditional clothes outside the house. The wife, however, is educated, drives a car, works with men, and even swims wearing a sweat shirt and pants. One cosmopolitan family wears Western clothes exclusively, eats "fast food," and prays informally rather than ritually, yet the husband does not allow his educated wife to drive. Differences exist even within the same family: one man lets his wife swim in public in a bikini, but his brother says he would divorce his wife if she were to swim at all. Divorce, more difficult in Afghanistan than in the United States, is becoming common here.

Despite such variation, language and cultural dissonance keep most Afghan refugees from socializing with Americans. Socializing almost exclusively with family members leads Americans to conclude that Afghans are uninterested in cohesive community action. Having recently brought their tribal orientation to the United States, there is much distrust between families. When asked why Afghans cluster in specific neighborhoods, an informant said, "We just want to see others like ourselves."

Immigration and Adjustment Issues

Afghan refugees have problems with English, employment, cultural conflict, children's education, and the absence of culturally appropriate health and social services.[4] More than 90% of Afghan families are supported by Aid to Families with Dependent Children. They are unwilling to give up its benefits, particularly Medi-Cal (California's Medicaid) for their large families in exchange for minimum wage jobs with no security. A resettlement counselor complained that Afghans come to California believing that "welfare is a must for making it in this country; they were told what to ask for before arriving by those already here."

Men have depression linked with a loss of status brought on by unemployment and changing family roles.[5,7] The traditional patriarchal role of the husband as the authority and breadwinner is devalued when they are unable or unwilling to obtain employment, especially if their wives take jobs, however menial. Most Afghans are downwardly mobile. Men from middle-class backgrounds are more willing to accept entry-level jobs than are well-educated or upper-class refugees, who frequently do not qualify for the kinds of work they did in Afghanistan—for example, physicians who are unable to pass the licensure examination because of finances, language problems, or outdated medical training. Some occupational problems are cultural, such as absenteeism on Fridays—the Sabbath—to attend the mosque or visit family.

Children learn English quickly and must often act as family spokespersons in relation to community institutions. Adolescent girls in particular are torn between traditional cultural values of modesty and chastity and behaving like their American peers.[4] One father, concerned about his daughter's physical education class, said,

> Our culture says we have to cover the entire body. Especially the swimming part is very insulting. I told the teacher to excuse my daughter from swimming. They ignored my request, which forced me to stop my daughter from taking that class. She was scored F, but deep in my heart I am happier about the F than her exposing her body in public.

Homebound women and elders are socially isolated and lonely. They miss the bustling social life of Afghanistan, which revolved around constant visiting. Here, visiting is constrained by distance, transportation problems, and the faster pace of American life. Older people have the most unhappiness and ill health. Many women and elders speak insufficient English to socialize with American neighbors, but even with English they describe Americans as "smiling and nice, but not friends."

Most women married young in Afghanistan (at 14 to 16 years) and have at least five or six children. They frequently appear older than the US norm for chronologic age: 40-year-old grandmothers have missing teeth or dentures. Coming to the United States separates polygynous families: a third wife feels "stranded" because she cannot go back home and her husband and co-wives cannot come to the United States from Pakistan unless they lie about being "sisters." Women who work face a triple burden of job, homemaker, and family mediator. Women are caught between their husbands' expectations that they behave traditionally and their own desires for more freedom and between their own traditional values and their children's rapid acculturation.

Cultural conflict is central to adjustment difficulties. A key difference between Afghan and American cultures is family interdependence versus individualism. Family life is the core of Afghan culture and psychological well-being. What Western psychiatrists call family "enmeshment" is normal family behavior. Each member is the responsibility of the entire family. Family obligations come before anything else, including the demands of American society. A parent, husband, or older sibling has the right to make demands: One woman described being telephoned by her older sister who was upset and asked her to "come over right away." Lack of transportation and other obligations made it difficult, but she went anyway because "I am younger, I have to obey." A newly arrived woman spent her days cooking and cleaning for her son. She became lonely, however, and insisted that he stay home from work to be with her; he was fired from his job.

Child Protective Services receives calls regarding possible child abuse in Afghan families, stemming from Afghan men's depression, alcohol abuse related to frustration with life in California, or the difference in disciplinary style. A young widow recounted,

> In Afghanistan, we discipline our children to respect their parents and elders, and, if they don't, we punish them; my 12-year-old told her teacher "my mom hits me"; the teacher called the Social Service Department, and they took my children away.

Because of this kind of incident, some Afghan parents have become afraid to discipline their children.

Health Problems in the United States

In 1985, in a medical record review of 59 new Afghan refugees served by the San Francisco General Hospital Medical Center Refugee Clinic, the most frequently diagnosed

conditions were found to be dental caries (41%), dermatologic disorders (39%), intestinal parasites (36%), gastrointestinal disorders (23%), and musculoskeletal pain (joints, back, 12%).[8] After the first year, physical complaints give way to psychological ones.

Motor vehicle injuries, too, are common; traffic accidents occur because of inadequate knowledge of the driving code and a lack of experience with urban driving. In addition, few Afghans wear seat belts. Observations by public health nurses, interpreters, and Afghan community members concur with our impressions of much active tuberculosis, diabetes mellitus, asthma, hypertension, and intestinal parasites. Birth control is a problem, and women do not want Papanicolaou smears and breast examinations.

A community mental health psychiatrist described Afghans as suffering "lots and lots of depression." Afghans themselves comment on the prevalence of "mental problems" in their community: "Afghans are sick because of thinking too much"; "Sadness is the sickness Afghans are faced with"; "They lost everything, members of their family, and the effects will remain forever"; "Whenever I see the good food cooked by my wife, I cannot enjoy it because I wonder whether my brothers and sisters in the refugee camp have enough food to survive"; and "The things they got from Afghanistan—murder, bombs—and the things they got here—children's freedom and not obeying, fear for children's future—all together make them mentally sick."

Posttraumatic Stress Disorder

Posttraumatic stress disorder is common among Afghans and is expressed in nightmares, sleep disorders, somatic complaints, depression, withdrawal, avoidance, loneliness, persecution reactions, apathy, and hopelessness.[9,10] Some refugees were imprisoned in Kabul, sometimes for several years, by the Communist regime. A number of the imprisoned were also tortured[11]: a 40-year-old physician's imprisonment resulted in hands that shake so much that he cannot work. Many escaped the country by walking for weeks over mountains while being shelled by Soviet helicopter gunships. These escapees were malnourished, suffered exposure to freezing weather, observed massive destruction, and experienced injuries and the death of family members along the way. A 50-year-old woman cannot sleep; she spends the night praying and often cries if someone speaks to her. Five years ago, after a missile attack on an apartment building, she picked her way through the scattered parts of 130 shattered bodies and saw a disembodied beating heart and an eyeball stuck to a tree like a leaf.

Health and Illness Beliefs

Afghans are concerned about their health. One woman said, "If you have health, the key to the whole city is in your hand, but if you are sick, what are you going to do with riches?" Most Dari words for health mean "whole," "wholeness," or "completeness."[12] Informants say that health is maintained through good habits: regular exercise, eating fresh food and a balanced diet, staying warm, and getting enough rest. Some illness can be prevented, Afghans believe, by living in accordance with the precepts of Islam, which strongly emphasize personal daily hygiene. One Afghan said, "Afghans are obsessive about cleanliness; we keep our bodies, our houses, and our children clean."

Concepts of purity and impurity are integrated into ideas of health and disease.[12] The ritual of ablution before prayer includes washing hands and arms, feet, face, nose, and inside the throat. If a person urinates, defecates, passes gas, falls asleep, vomits, or bleeds, he or she becomes impure and must wash again. After sexual intercourse, the entire body, head to toe, needs to be washed before the person is fit to pray. Women are prohibited from prayer or fasting during menstruation and must perform a full purification ritual seven days after the cessation of bleeding.

Illness may be interpreted as the will of God and should be "borne with patience and steadfastness as it cleanses one of individual sins, and God will have mercy on a sick person." The meaning of suffering and the purifying effect of illness, however, do not mean that the sick person should avoid treatment. Illness is thought to result from not adhering to the principles of Islam. An older woman who became acutely ill after someone told her that she had inadvertently eaten pizza with pork said, "I was very stupid. It is against Islam to eat pork, it is forbidden to us by our Book (*Qur'an*). If we eat it, it means we are against our religion."

Prayer in general is considered useful for healing, but religious leaders and healers know specific effective verses of the Koran for specific illnesses. Ritual prayer includes the following: *ta'wiz*—verse written on paper that is covered with clean cloth and worn like a necklace by a baby or ill person; *shuist*—verse written on paper that is then soaked in water and the water drunk; and *dudi*—verse written on paper and burned with rue near the patient so that the smoke will ward off evil spirits and kill germs.[12]

Natural Illness

Natural (physical or biologic) illness is caused by things that exist in nature, such as "germs," dirt, cold, or wind. It is believed that people are more vulnerable to colds or flu during the change of seasons.[12] Some Afghans explain that illness is associated with not taking proper care of the body:

> When we eat lamb and rice for lunch, it is not digestible here because we don't have time to walk and exercise after, so the amount of cholesterol goes up and blood pressure goes up, creating the possibility of heart disease.

Traditional Afghan medical beliefs emphasize the humoral concepts of Arabic-Persian medicine, which originated with the Greeks and were carried to Central Asia with the spread of Islam.[12] "Hot" and "cold" are qualities of food, drink, and medicinal herbs, of individual human nature—related to age, sex, and temperament—and of illnesses. Illness results from humoral imbalance and is classified as either hot or cold. Hot illnesses, such as fever or measles, are treated with a diet emphasizing cold foods and medicines; cold illnesses, which include arthritis, malaria, and chickenpox, are treated with hot foods and medicines.[13]

Both traditional and Western biomedical treatments are used. There is no strict hierarchy of resort, and Afghans often use several kinds of treatments at once. Mild natural illnesses are treated with home remedies and dietary means alone, and biomedical care is added for more severe illnesses. In most families there is an older woman who knows how to prepare home remedies: "Medicine that I make by myself from the roots of the bushes I learned from my mother, and now my family learns from me." Home remedies include a variety of herbs, roots, and "bushes" available in Afghan, Iranian, and Indian food stores. Natural illnesses are often also treated by religious means, such as prayer or *ta'wiz*.

Supernatural Illness

Jinns or other supernatural beings can cause illness, as can "the evil eye" or punishment from God. Mentioned in the *Qur'an,* jinns are described as ghosts or spirits. Some are good and some are bad, but people generally do not like them. Epilepsy is an example of an illness caused by a jinn.

The evil eye, *nazar,* is the belief that someone can cause illness or harm by looking at another person. Although it can originate with anyone, a more powerful "gaze" is thought to come from green-eyed, impure, or ill people. *Nazar* can be unintentionally caused by expressing excessive admiration or love for another without remembering to say a preventive phrase, such as "In the name of God." Intentional *nazar* is cast out of jealousy, envy, or enmity and is meant to hurt another person or the person's property.[12] *Nazar*-caused illness is distinguished from other illnesses by its sudden onset. Susceptible people, such as children, beautiful women, or fortunate people, can be protected through charms or amulets, such as blue stones or beads. *Espand* (wild rue) can also be used to prevent *nazar:* "When burned in the fireplace," explained one woman, "*espand* forces the evil spirits out; the sounds of the seeds popping are like the sounds of eyes popping." There are many curing rituals for *nazar,* including some that use eggs, other white substances, prayers, or verses.[12]

Practice Implications

Providing culturally sensitive health care to Afghans is similar to providing care for Middle Eastern immigrants. These groups share the same kinds of expectations and behavior: "doctor shopping," grilling a physician to see if he or she is competent, expecting injections or pills, storing bags of medicines at home to be used for other family members, and missing appointments because of social obligations or lack of transportation, interpreters, or child care. Suggestions for disclosing grave information, using a personal approach, establishing trust through continuity of care, and using cultural interpreters are described elsewhere.[14-16]*

Access to Services

Afghans have poor access to health care in general and few culturally specific services. Language is a barrier, and few health facilities employ Afghan translators. Although most refugees have Medi-Cal, they have difficulty locating physicians who take it. Seeking care is complicated; one Afghan complained that several people are required to "find the doctor who accepts Medi-Cal, make the appointment, translate, give ride to us."

Although most Afghans agree that mental health is a problem in their community, families seek such services only as a last resort. Afghans do not value "talk therapy," preferring a medicine for a "quick cure." Even when culturally sensitive services are available, such as a local Afghan psychotherapist, many Afghans are still loathe to use such services. They are afraid of gossip, losing face, or sharing sensitive "personal" information, such as nearly anything about the family. If the problem is seen as shameful—for some men, this means almost anything that could show "weakness"—both the problem itself and admitting it are difficult. Some Afghans would see Iranian therapists, whose language and culture are sufficiently similar to allow understanding, but most of these therapists do not take Medi-Cal. Whatever the background, Afghans prefer a competent middle-aged and gender-matched therapist, although perceived competency is more important than gender.

Gender and Communication Issues

Because of traditional male-female social restrictions, women patients are more comfortable with women physicians, especially for obstetric and gynecologic concerns. If female health professionals are unavailable, women patients will see male obstetricians and gynecologists recommended by a trusted interpreter or other women. Male physicians, however, should restrict touch to that which is necessary for examination, except for shaking hands, and should be careful to restrict direct eye contact.

Afghans, like Middle Eastern immigrants, have a cultural communication style that is often misinterpreted by American physicians as being devious or insincere. Ritual courtesy is practiced between people of unequal status; this appears as an easy acceptance of medical regimens when it is really simply showing respect.[17] Afghans avoid saying "no" directly and do not like to hear "no" being said to them. Histories are difficult to take "efficiently" from Afghans, who communicate by means of stories.[14] Health care professionals must also deal with the whole family, rather than with just the patient.

In many cases only a family member, often a child, is available to translate. This situation is undesirable because of a lack of vocabulary and the tendency to hold back information because of embarrassment. If there is no one else to translate, it is helpful to first ask the parent, "Do you permit your child to translate?" to give the adult patient some say in a self-esteem–reducing situation.

Health providers should make every effort to secure the help of trained bicultural, bilingual interpreters. Ideally, interpreters should be

- Gender matched to the patient, but if only one is available, a woman is preferable;
- Married;
- Of good reputation;
- Not too young;
- Not "too modern" or "too traditional"; and
- Not identified with a political party, otherwise they might not be trusted with important information.

Remember that interpreters work with three or four languages (medical terminology, English, Dari, Pashto), several accents, and the patient's inadequate knowledge of anatomy. For example, the patient says "I have kidney pain" yet points to his chest or says "liver" when he means "heart." If the interpreter uses the physician's style of short direct questions, an Afghan patient will probably perceive the interpreter as impolite and withhold information; on the other hand, an interpreter who communicates appropriately with Afghans irritates an impatient American health provider.

When working with an interpreter, talk directly to the patient and do not refer to the patient in the third person. Afghans do not like direct personal questions, especially regarding the family, and interpreters know how to phrase questions and get information in a polite, culturally acceptable manner. A public health nurse with 15 years' experience working with refugees comments:

> You have to trust your interpreters, they are your lifeline. Tell them the information you want, and trust that they will get it, even if it takes two hours

*See also L. Haffner, "Translation Is Not Enough—Interpreting in a Medical Setting," on pages 255-259 of this issue.

and many stories. Health providers don't understand how different their refugee clients think and behave; they expect to get the information they need right away.

Traditional Health Beliefs and Remedies

Many Afghans, especially men, who are ashamed of believing something old-fashioned, may not admit to traditional beliefs and practices. Physicians should ask about the use of traditional remedies, however, because of possible interactions with prescribed medications or their influence on symptoms. In one case, an herbal concoction used for a cold proved to be a powerful sedative. Because of fear of the "evil eye," health professionals should be careful about compliments, unless they add such statements as "Thanks to God." Afghan patients are reassured by following a statement about the potential for recovery with an expression like "knock wood" or "God willing."

Health Education and Community Support Services

Afghans need health education in relation to emergencies and acute care, such as how to dial 911, basic cardiopulmonary resuscitation, what to do when a child is sick, and how to use a first-aid kit. They also need information on immunizations, reading labels and the correct use of prescription and over-the-counter medicines, poisons, child safety, and basic knowledge of how the body works.

Because many of the symptoms presented by Afghan patients are stress related, health professionals should locate or lobby for community support services for this population. Psychosomatic symptoms of many Afghan women and older persons may be related to their social isolation. A successful project was started through inviting seven unrelated older women to several weekly picnics in a park. The women became friends and now take the initiative for organizing weekly outings, depending on the initiators only for transportation. Striking changes have been observed: one woman was originally so "weak" that she could not get off the couch or raise her teacup to her mouth; recently, she walked three miles around a lake.

In conclusion, physicians should attempt to assess their Afghan patients within the sociocultural context of their lives in the United States, including inquiring about their journey to this country. Past traumatic experiences, cultural conflict, economic problems, family strain, or loneliness may be the key to symptoms for which medication can do little.

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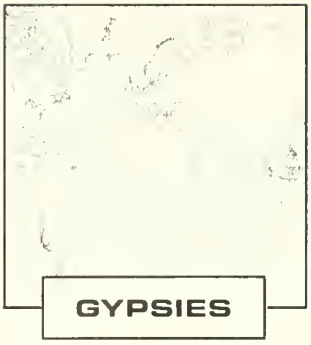
- Gypsies, widely distributed throughout Europe, migrated to the United States at the end of the 19th century
- It is estimated that there are between 200,000 and 500,000 Gypsies in the US
- There are several culturally distinct groups, of which the Rom is the largest



Cross-cultural Medicine
A Decade Later

Gypsies and Health Care

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Gypsies in the United States are not a healthy group. They have a high incidence of heart disease, diabetes mellitus, and hypertension. When they seek medical care, Gypsies often come into conflict with medical personnel who find their behavior confusing, demanding, and chaotic. For their part, Gypsies are often suspicious of non-Gypsy people and institutions, viewing them as a source of disease and uncleanliness. Gypsy ideas about health and illness are closely related to notions of good and bad fortune, purity and impurity, and inclusion and exclusion from the group. These basic concepts affect everyday life, including the way Gypsies deal with eating and washing, physicians and hospitals, the diagnosis of illness, shopping around for cures, and coping with birth and death.

(Sutherland A: Gypsies and health care, *In* Cross-cultural Medicine [Special Issue]. West J Med 1992 Sep; 157:276-280)

Gypsies are a largely unknown ethnic population in the United States. Lacking census data, most estimates suggest there are between 200,000 and 500,000 members of various Gypsy groups living in all regions of the United States. Not all Gypsies belong to the same group or speak the same dialect or language. The data presented here refer to the largest group, the Rom, which is the group physicians are most likely to see and to recognize as Gypsy.[1] The Rom live all over the United States. The specific group this article is based on live in the San Francisco Bay Area of California. The Rom are originally from India, migrated through the Middle East and Europe over the past 800 years, and arrived in the United States primarily at the end of the 19th century. The Rom speak Romany as a first language and English as a second language. Older Rom are generally not literate, but younger members of the family usually have some schooling and can read important documents to older members.

Although most Americans hardly know that Gypsies live in their cities, the medical profession is usually aware of them. This is because Gypsies are generally not healthy and because they are assertive in seeking medical care. Gypsies have an unusual ability to maneuver within a complex medical system and to get attention from medical personnel. The Gypsy "style" of seeking help is often frustrating and confusing to health care professionals. Gypsies often request specific "famous name" physicians and demand specific treatment they have heard of even when the treatment or specific physician is inappropriate. Gypsies frequently request specific colored pills that they share with their relatives. They prefer older, "big" (well-known) physicians over younger ones. They often do not comply with preventive and long-term treatment. When a relative is sick, they come to the hospital in alarmingly large numbers, sometimes camp on hospital grounds, disregard visiting rules, and generally create chaos in the corridors of the hospital. Hospital personnel are often at a loss in knowing how to deal with Gypsies.

Gypsies can be cooperative, interesting patients, however. They respect authority in their own families, they are eager to learn about the best treatment for themselves and their relatives, and they have a large support network of relatives. All of these factors can be called on by medical professionals to assist them in providing treatment to Gypsies while reducing the disruption that results from a sick Gypsy's desire to have relatives nearby.

In this article I provide information about Gypsy culture that will be useful for understanding how to interact with them in medical situations. This article contains guidelines, but not every Gypsy follows every single custom or rule. Families and individual members have varied practices. Some Gypsies are more old-fashioned than others; some are more fastidious; some, generally older ones, are more informed; and some are sicker and have more experience with physicians. Nonetheless, these general guidelines should ease some of the frustration between Gypsy patients and health professionals.

Gypsy Culture

Gypsies live in urban areas, usually on main streets, in the poorer parts of towns. They are not always recognizable as such, especially the men who wear American clothes; however, women, in particular older women, often wear long colorful skirts and low-cut sleeveless blouses. Gypsies often prefer to pass as another ethnic group and may claim to be American Indian, Mexican, or Romanian. They are accustomed to discrimination and stereotyping by those who often see them either romantically as free spirits or as contemptible thieves. Neither stereotype is accurate. If a medical professional indicates that it would help to know if a patient is Gypsy, the family may freely admit to it.

Gypsies live in households with somewhat fluid member-

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ship because they generally belong to large extended families. Dating back to the days when they all shared one camp, members of extended families will eat and sleep at each other's homes as if they were their own. The men work in groups of relatives and friends. Their usual work involves soliciting body and fender repair jobs, buying and selling cars, or helping women with their fortune-telling businesses. The women (mothers, daughters, and daughters-in-law) often share a storefront office or room at the front of a house, where they tell fortunes. Gypsies prefer to keep to themselves and to avoid contact with non-Gypsies. As a cultural group, they have survived hundreds of years living by their wits.

Illness Is Social

For Gypsies, illness is not just the concern of the individual, it is a problem of broader social importance. A serious illness always elicits deep concern from a wide circle of relatives willing to drop everything and rush to the bedside of the stricken. The gathering of Gypsies in the vicinity of a seriously ill person is partly socially mandated by custom but also is a genuine expression of concern for both the afflicted and his or her immediate relatives. Families coming together when someone is ill is one of the strongest values in Gypsy culture.

A knowledge of certain basic beliefs and behaviors of Gypsies in relation to sickness and health and the sociocultural context of health care is essential to effectively interact with Gypsies. The social context of Gypsy medical and religious knowledge begins with Gypsy attitudes in general toward health and illness, auspiciousness and inauspiciousness, and cleanliness and uncleanliness.[2] These attitudes are reflected in certain key concepts, presented in complementary opposition in Table 1.

TABLE 1.—*Key Concepts in Gypsy Thought*

Positive Concepts	*Negative Concepts*
Romonio (social order)	
Rom (Gypsy)	*Goje* (non-Gypsy)
Traveling	Sedentary
Sostimos (good health)	*Noswolemos* (illness)
BaXt (good fortune)	*Prikozo* (bad luck)
Wuzho (purity)	*Morime* (impurity; exclusion)

Fortune and Health

Good fortune and good health are closely associated for Gypsies, as expressed in their most common blessing, "May God give you luck and health." Those who enjoy good health also have been blessed with good fortune; those who are ill have lost their good luck. To some extent everyone can influence their own fortunes. By their actions they either promote their own health or cause their own illness. Illness can be caused by actions that are considered contaminating or polluting. Returning to a state of purity and conforming to correct social behavior are necessary to cure these conditions. For example, a young person who exhibits rebellious behavior and may be in danger of pollution through illicit sexual relations can be "cured" by marriage.

Perhaps the most frustrating belief physicians encounter is that the larger a person is, the luckier, healthier, and happier that person will be. A fat person is perceived as healthy and fortunate, and a thin person is pitied as either ill or too poor to eat, both of which indicate a lack of good luck. Wealth is also partly attributed to luck because although each family develops similar economic skills, some are more fortunate than others. Some families enjoy good health, grow to a large size, and prosper, whereas others are plagued with illness, family troubles, and economic failure. In such a situation persons must take action to change their fate. Personal cleanliness, proper social attitudes, and behavior—generosity and virtue—should bring good luck. In a more general sense, traveling as opposed to living in one place is considered auspicious.

Marime, meaning polluted, defiled, or unclean, is used to indicate uncleanliness or impurity of a physical as well as a ritual or moral nature. To be "clean," the top half of the body from the waist up ideally must be kept separate from the bottom half of the body, which is considered polluted and is an area associated with feelings of shame.[3] The source of pollution of the lower body is the genitoanal area and its emissions and secretions. Secretions from the upper half of the body are not polluting or shameful. For example, spittle is viewed as a clean and curative substance that may be used to clean cuts or scratches. This viewpoint conflicts with medical practice, which sees spittle as a possible source of contagion. Separate soap and towels are allocated for use on either the upper or the lower part of the body, and they must not be allowed to mix. Bathing in a hospital can be easily accommodated to Gypsy beliefs by providing them with separate soaps and towels for the upper and lower parts of the body.

A failure to keep the two sections of the body separate in everyday living can result in serious illness. A large number of practical guidelines are necessary to keep the upper half of the body separate and pure. At the least, it is important to wash the hands after touching the lower body and before touching the upper body. Body separation is a general cultural ideal that comes into play more in public situations than in private ones, and it has implications for a physician wishing to examine the lower body. Most Gypsy women will not agree to a gynecologic examination or a Papanicolaou smear unless the necessity of the procedure is clearly explained as essential to a woman's well-being.

Marime can also mean rejection because to become physically or morally impure could mean being rejected by the entire group. Rejection is a serious punishment for a Gypsy because it means social isolation.

Marime and Non-Gypsies

The use of *marime* as a defining term for a whole series of social boundaries gives it much importance for the Rom. The most important boundary is that between Gypsy and non-Gypsy. Because they do not observe body separation, non-Gypsies are a source of impurity and disease. Public places where non-Gypsies predominate such as public toilets, hospitals, buses, schools, offices, jails, and non-Gypsy homes are also potential sources of disease. All these places are less "clean" than the home of a Gypsy or open outdoor spaces such as parks and woods. When they must be in non-Gypsy places, Gypsies generally avoid touching as many impure surfaces as possible, but, of course, prolonged occupation of a non-Gypsy place such as a hospital means certain impurity. In this case the person tries to lessen the pollution risk by using disposable paper cups, plates, and towels—that is, things not used by non-Gypsies.

Age-Related Cleanliness

Concern for a person's health begins at birth and is most active during the days or weeks of confinement (from 9 days to 6 weeks) of the mother. In the past, infant mortality for Gypsies has been high. This may be somewhat improved nowadays because more women give birth in hospitals; however, the crucial period of prenatal care is still entirely neglected because few women will accept a vaginal examination. One of the reasons Gypsies have turned to hospital birth is the advantage to them of avoiding the impure birth substances.

Gypsies recognize that a baby is vulnerable in the first weeks of life and take precautions to protect the child. A new baby is immediately swaddled tightly and handled only by his or her mother. The woman avoids certain foods, such as green vegetables and tomatoes, so that the nursing baby will not get colic. The child's navel is carefully cleaned and protected with ashes, and amulets are sewn into the baby's clothing for protection. In the first weeks at night, no member of the family is allowed to go in and out, and all windows and doors are kept shut lest a spirit of death, called "the night," enters to harm the baby. Crying and fear are prevented in a child by placing a small piece of *johai* ("ghost vomit," a curative substance) on their tongue. Visitors are carefully watched lest they give the baby the evil eye. If the baby fusses or becomes ill, the giver of the evil eye must make a cross with spittle on the forehead of the baby.

If despite these precautions a baby dies, this is bad luck for the parents. They must avoid the baby's body, which is buried in a secret place by the grandparents. Another way to avoid the bad luck of the death of a baby is to leave the funeral and burial to the hospital authorities.

After the period of pollution of birth has passed (more or less 6 weeks), children are considered basically pure in body and action. They can enjoy freedom from most social restraints and are not expected to understand or demonstrate "shame" in their actions. Physical contacts defiling to adults are not necessarily defiling to children, who need not take many of the precautions that adults do to ensure cleanliness in their daily lives. Children, for example, may eat food handled and prepared by non-Gypsies that postpuberty juveniles would reject.

At puberty, boys and girls are introduced to the idea of personal shame. Now both their bodies and their actions will be judged in terms of control of their own polluting secretions (menstrual blood, semen) and of "shameful" and polluting actions (sexual contact). The control of sexual relations and body cleanliness is modified by marriage and childbirth, but basically such controls last throughout married life until old age.

Women have a particular need to keep clean. Menstruation, for example, is surrounded by a number of rules to control the ill effects of this potentially polluting bodily function. When a girl first menstruates she is introduced to shame and must observe the washing, dressing, cooking, eating, and behavioral rules of adult women, partly for her own protection and partly for the protection of men. Her clothes must be washed separately from those of men and children, and she cannot cook food for others during menstruation. She must show respect to men by not passing in front of them, stepping over their clothes, or allowing her skirts to touch them.

At old age, after menopause and when sexual relations are assumed to have ceased, many of these regulations are relaxed. The aged are venerated and respected persons, both because they are politically powerful (political authority is vested in the aged) and because they now enjoy a "clean" status. When in contact with a group of Gypsies, it is always wise to seek out older authority figures and to communicate problems in their presence because they have authority and exert influence over younger Gypsies. Also, without the approval of older relatives, many young Gypsies will not agree to medical procedures considered risky.

Food and Health

Gypsies try to eat only food that is known to be pure and clean. Consequently, there are many regulations regarding the preparation and handling of food. There are no foods that are always prohibited, although some adult Gypsies fast on Fridays. Some foods—pepper, salt, vinegar, garlic, and onions—are considered lucky. To eat them encourages good health.

Eating together is imbued with great social significance. To share food with someone demonstrates respect, friendship, and acknowledgement of their cleanliness. Refusing to share food is a serious affront, implying a person is not pure and clean. The most serious punishment Gypsies as a group can impose on anyone is to refuse to eat with the person. To be prohibited commensality is social death. All rituals at which the Gypsies express important unifying social values involve the sharing of food at a feast.

All food must be carefully prepared to avoid any *marime* contacts. Cooking and eating utensils are always washed in a special separate basin reserved only for that purpose. In many households, a separate soap is reserved for food-related items, and even the hands are washed only with that soap before handling food. Women in birth confinement and menstruating women do not handle food. Food prepared by non-Gypsies is *marime* and is avoided. This avoidance is not always possible, such as when in a hospital, but it can be aided by eating wrapped take-away foods, drinking from cartons or bottles, and using disposable eating implements. Gypsies may simply eat with their hands rather than use utensils that may not have been properly washed.

Causes of Illness

Gypsies make a distinction between illnesses that originate from the non-Gypsies (*gaje*) and illnesses that are exclusively part of their own world. The former can be cured by non-Gypsy doctors, but the latter can only be tackled by the *drabarni*, their own medical practitioners. A knowledge of Gypsy medicine is the prerogative almost exclusively of the oldest women. They are both respected and feared because of this knowledge.

Gypsies do not have a scientific understanding of how the body functions. To them American physicians simply have a special knowledge of (*gaje*) illnesses and cures, a store of lore on medicines, and diagnostic and curing techniques. Not all physicians have the same knowledge or ability. To a Gypsy, a "big" doctor is one who cures, and a bad doctor is one whose medicine does not work.

Hospitals are feared and avoided whenever possible. Most Gypsies will go to a hospital only if they are in serious danger of dying or if they view the situation as a crisis. Furthermore, a hospital is a hostile place for the Gypsies, full of non-Gypsies, unclean, and completely removed from

TABLE 2.—*Disease Causation and Treatment*

Disease	*Cause*	*Cure*
***Gaje* (non-Gypsy) diseases**		
Flu, "fevers," gonorrhea, syphilis, hernias, hemorrhoids	*Morime* from contact with *goje;* germs	Avoid *goje; goje* physicians
Gypsy diseases		
Mental illness; mental retardation	Denial of cultural rules	Observe cultural rules, such as marriage
Grave illness, such as polio, serious influenza, pneumonia, and hemorrhages	*Momioro,* a spirit who visits places that are unclean and brings illness	*Johoi* ("ghost vomit"), *Fuligo septico,* a slime mold, is curative
Tosco (nerves); convulsions	*O Beng,* the Devil, the source of evil	*Khontino drob* ("Devil's dung") or asafetida
General illness and bad luck (*prikozo*)	*Mule,* spirits or ghosts; not necessarily harmful, but Gypsies are afraid of them	Prevented by showing respect to the dead; observing *pomono* (death ritual); avoiding places *mule* may visit; traveling

Gypsy society. Too few visitors are allowed, so for the Gypsies, who want to be with their kin when ill, a hospital is close to a state of exile from their own society. For these reasons, many Gypsies suffer great pain rather than go to a hospital. If they have to be admitted, the one thing they know for certain is that they do not want to be alone, to be without their relatives.

Gypsy and non-Gypsy diseases overlap, but their causes are different (Table 2). Most Gypsies prefer to try several different cures for any single illness to combat the different causes. A person who has convulsions, for example, may be rushed to a hospital where a physician can attend but will also be given asafetida by relatives. Physicians, therefore, are not in competition with Gypsy *drabarni.*

Health Status of Gypsies

Many Gypsies claim that they are sicker now than they used to be. They believe it is because they travel less and live in houses instead of separate from non-Gypsies in camps. They think that the closer contact with non-Gypsies is having a deleterious effect on their health. Recent work on the medical condition of Gypsies would indicate that their medical problems are in fact serious.[4] In a study of 58 Gypsies in the Boston area, Thomas found that 41 of 56 (73%) had hypertension, 24 of 52 (46%) diabetes mellitus, 32 of 40 (80%) hypertriglyceridemia, 26 of 39 (67%) hypercholesterolemia, 20 of 51 (39%) occlusive vascular disease, and 8 of 40 (20%) chronic renal insufficiency. A combination of diet, which is extremely high in fat, and genetics could be leading to the high cholesterol levels and hypertension. In this group, 50 (86%) smoked cigarettes and 49 (84%) were obese. The life expectancy of a Gypsy in the United States is between 48 and 55 years.[5]

To combat non-Gypsy diseases, the Gypsies logically turn to non-Gypsy physicians and hospitals. Although they are eager to try any cure that they think might work, they are suspicious of physicians and tend to "shop around." A physician who acquires the reputation of being effective will find Gypsy patients flocking to the office. Physicians whose Gypsy patients die under their care will probably never see another in their practice.

Surgery is feared, especially when general anesthesia is required, as Gypsies believe a person under anesthesia undergoes a "little death." Thus, Gypsies will gather around the bedside to muster support and help the patient come out of the anesthesia.

Despite their fear of hospitals, Gypsies are in general extremely knowledgeable of hospital procedure. They know what services are available and who are the best physicians for specific problems. They learn of famous clinics and learn the complicated hospital regulations, how to get around them, and how to get what they want. One study concluded that Gypsies receive better medical care than other urban minorities because they have figured out effective ways to use medical services.[6] In the same way that they are willing to try physicians and hospitals to cure them, they will also try cures and medicines advertised by Mexican *curanderos,* faith healers, and patented miracle cures. These are all *gaje* remedies. Nothing that might work is to be scorned.

Gypsy diseases have no connection with non-Gypsies or with germs and therefore cannot be cured by non-Gypsy physicians. For these diseases the Gypsies must turn to their own knowledge and their own medical practitioners, the *drabarni* (literally, "women who have knowledge of medicines"). The knowledge of spirits and medicines that old women have is a great source of power for them.

Serious Gypsy diseases are caused either by a spirit called *Mamioro* or the Devil. *Mamioro,* a specific spirit who has become a disease carrier, causes illness simply by visiting the homes of Gypsies. Fortunately, she only visits dirty houses, so by keeping a clean house, the Gypsy can keep her away. *Johai,* her vomit, is found most frequently in garbage dumps, and it is the most powerful and valuable cure the Gypsies have.*

Several important diseases are caused by the Devil. *Tosca* is a disease that the Gypsies translate as "nerves." People who are nervous, fidgety, and worry excessively have *tosca.* A lot of Gypsies get *tosca,* especially the less aggressive and more sensitive ones who find it hard to keep up with the demanding, noisy, fast pace of Gypsy social life. *Khantino drab* will cure *tosca. Khantino drab* is also said to be found near the place where a person has been seized with a convulsion or epileptic seizure. It is believed that convulsions occur when a person is possessed by the Devil and that usually the Devil defecates during the convulsion. Locating the *Khantino drab* and giving it to the convulsed person will make the devil *marime* and drive him away.

Death

Gypsies can never be sure that they have done everything possible to keep pure, to promote auspiciousness, and in general to live up to the ideals of correct behavior; therefore, it is not surprising when someone becomes ill or suffers

*Rena Gropper, PhD, Professor of Anthropology at Hunter College and a gypsiologist, discovered "ghost vomit" on some wood chips in her garden in New York City. Thomas H. Delendick, PhD, associate taxonomist at the Brooklyn Botanic Garden, identified it as a slime mold, *Fuligo septica.* A literature search showed that heretofore there had been no known economic or folklore uses of this slime mold (written communication, July 1983).

misfortune. For the Gypsies, illness and death are not only a personal crisis, they introduce a social crisis as well. Reporters, physicians, hospital staff, social workers, and police are all aware of a great happening when a Gypsy becomes seriously ill and dies. When they ask what is going on, they may be told, "a Gypsy king (queen, prince) has died." This reply is a way of satisfying reporters and providing a reasonable explanation to hospital staff and police of why the Gypsies are flocking into town in large numbers, camping on hospital grounds, and in general breaking rules and creating havoc. Although there are no kings and queens, only leaders of the large Gypsy extended family, death is a major crisis in a Gypsy family that must be dealt with in ritual.

When a young person dies unexpectedly, the relatives are so grief-stricken that their behavior can become extremely wild. In one case, after the accidental death of a young man, the relatives were so distraught that they threatened physicians for "letting him die." The relatives scratched their faces, drawing blood, beat themselves on the chest and head, wailed, and screamed. This behavior was an expression of extreme grief. Even in the case of a death that has been anticipated, however, it is culturally acceptable for relatives to moan and shout out to the deceased, scratch their faces, or pull out their own hair.

Death at an old age is generally perceived as part of the natural and acceptable course of events, and the attitudes and feelings toward the death of an old person are very different from those toward early death. The main preoccupation of the relatives of an old person, as well as the dying person, is to see that all preparations for the person's eventual demise have been arranged. For the Lowara Gypsies, Yoors said, "the Gypsies yearned for what they called 'a great death' for which they could prepare and which they could share with their households, relatives and friends. They feared most that kind of death which came when one was unprepared."[7]

John Davis, also known as Rattlesnake Pete, had a "great" death. His funeral was the greatest spectacle since Big George Adams hired an entire movie studio to provide props for his funeral in Los Angeles. John Davis had a brass band playing Dixieland in the funeral cortege, a horse-drawn hearse complete with black enameled scrollwork and silver lanterns and drawn by two grey Appaloosas. His grave was a red-carpeted crypt with a chandelier inside in a grave site surrounded by full-sized statues of the Apostles. In front of the casket was a flower arbor with the words "Welcome to Heaven, John Davis," in gold letters. He also had flowers in the shape of his favorite fishing chair with a pole and line dangling into a flower-edged pool, the American flag, a clock with the time of his death, a car, an airplane, and a ship (because he liked to travel), a barrel of beer and beer mugs (he liked a drink), and a little white house (he was a property owner). The newspaper the next day ran a picture of the funeral cortege with the caption, "Death of a Gypsy King" (Janet Tompkins, Contra Costa County Social Service, written communication, July 1976).

Conclusions

To help physicians and hospital personnel interact effectively with Gypsies, I have some specific suggestions.

- Older relatives have an important role in the decision-making process of a patient. Try to include them and treat them with the respect they are due as elders in the community. Older relatives can be of great help in ensuring the cooperation of younger ones.
- Gypsies can alternate rapidly between moods or styles of interpersonal interaction from extreme assertion to plaintive begging. Medical personnel should appeal to the strong desire of Gypsies to obtain the best medical treatment and assure them that cooperation will work best for them.
- English is a second language. Explain clearly without resorting to too many technical terms the procedures the patient will undergo. Then ask if there is anything that is against the patient's religion. If there is something they do not want done, explain why it is necessary for their health or allow them to forego it.
- Many Gypsies cannot read, but it would be a mistake to assume that they are therefore less intelligent. Read important instructions (particularly at intake) to a patient or ask a translator to read out loud to the patient. They are accustomed to dealing with complex bureaucracies and policies.
- Gypsies accept emergency measures more readily than they accept proscriptions to undertake changes in diet or lifestyle; however, instruction in long-term health goals is crucial. They need education on the connection between diets high in animal fats, heavy smoking, drinking, and no exercise and the health problems they cause.
- A Gypsy patient does not want to be alone and will be fearful and agitated if forced to be without family. Allowing some relatives in the room with the patient on a rotation basis will keep the chaos to a minimum. Allow someone to stay overnight with the patient. If the patient is dying, it is essential that relatives be allowed to be present at the moment of death.

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- American Indians are an indigenous, heterogeneous population with over 500 recognized tribes, bands, or Alaskan Native villages
- Over half (54%) now live off reservations
- Rural to urban migration was given great impetus by World War II and the federal policies of the Eisenhower era

Cross-cultural Medicine
A Decade Later

Health and Aging of Urban American Indians

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Although half of the American Indian population resides off the reservation, mostly in the western states, research on the health of urban American Indians remains sparse. American Indians living in urban areas are not eligible for the federally mandated health care provided by the Indian Health Service and receive health care services in a variety of settings. This population is at high risk for many health problems, especially cardiovascular disease and diabetes mellitus. Social, cultural, and economic barriers that impede access to health care for this group, particularly for elders living in an urban setting, could be reduced if physicians improved their understanding of and communication with American Indian patients.

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Urban American Indians have been called the "invisible minority" because their conditions and needs are not generally recognized in comparison to those of other ethnic minority populations. For over a decade, more than half (54%) of American Indians have lived outside of reservation communities. In this article I review the health status of American Indians, including misperceptions that affect their access to health care; describe their migration to urban centers; report on general health findings of elderly urban Indians; discuss approaches to relating to American Indian patients; and examine in depth the population of older urban American Indians and their prospects for health care.

The term "American Indian" is used here to refer to the indigenous peoples of North America. This term is preferred, particularly by elders of this population, to the term "Native American," which under certain federal legislation includes native Hawaiians, Samoans, and other Pacific Islanders.

The American Indian population is extremely heterogeneous: There are nearly 300 federally recognized reservations; 500 recognized tribes, bands, or Alaskan Native villages; and an estimated 100 tribes that do not benefit from federally recognized status. There is little public understanding or awareness of this cultural diversity and of contemporary American Indian peoples and their concerns.[1] The public is most familiar with northern Plains cultures (for example, the Lakota), thanks to Hollywood movies such as *Dances With Wolves*, and with cultures that have become strongly identified with their arts in a commercial context, such as Navajo weaving, Pueblo pottery, or Kwakiutl carvings. Different geographic regions host widely diverse American Indian societies.

Today, 150 native languages continue to be used. Just as there is no single American Indian language, there is no single cultural tradition or style of dress. In urban areas, tribal differences may not be apparent because a pan-Indian identity unifies many community-wide activities. Distinct cultural values and traditions, however, continue to provide a positive source of ethnic identity. A stereotype of "the American Indian" is unwarranted.

History of Urban Migration

The massive migration of American Indians to urban settings has been ongoing since the beginning of this century. From 1920 to 1950 a slow but steady migration took place from poverty-stricken rural reservations to the cities, which offered greater employment opportunities.[2] Participation in the military and the defense industry during World War II speeded up this migration process, as did the federal policies of the Eisenhower era.[3,4] By 1977, 50% of all American Indians lived off the reservation. Now more than half of the entire American Indian population lives in the western states, with the greatest number in California cities.

The favorable climate and the expanding labor market of West Coast cities attracted American Indians from across the nation. This accounts for the great heterogeneity of American Indians in Los Angeles compared with the relatively homogeneous population in Midwestern cities such as Minneapolis. The Los Angeles City and County Native American Indian Commission estimates that it represents members of 200 tribes.

Relocation from small indigenous communities to large industrial centers has created and exacerbated social problems for a portion of the migrating population. Numerous studies focused almost exclusively on these problems.[5] Such social deviation was not universal among urban American Indians, however. Price noted an important difference between those American Indians who had been relocated to Los

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Angeles by the Bureau of Indian Affairs and those who chose to live in southern California on their own initiative: The latter tended to be more successful.[6]

A difficult area of adjustment for some American Indians was getting health care in an urban setting. Eligibility for federally mandated health care provided by the Indian Health Service expires after 180 days of residence off the reservation,[7,8] and many American Indian migrants are unfamiliar with any other system of health care.[9] Recognizing this problem, the Indian Health Care Improvement Act of 1976 authorized the Indian Health Service to allocate funds for the establishment of health clinics by urban American Indian organizations. These urban Indian health clinics provide a health care option where many access barriers have been reduced through such practices as American Indian staffing, outreach by community health representatives, free transportation to the clinic, and educational programs. Although patient visits reached low levels in the late 1980s, in recent years both the amount of appropriations and the number of patient visits have increased. From 1989 to 1990, the levels of appropriations and workload increased more than 33%, with $13 million allocated for 570,000 patient visits (a return to the level of services provided in the early 1980s) for medical or dental treatment, community services, nutrition and health education, optometric services, mental health services, and substance abuse counseling.[10]

Some urban clinics have diversified their funding sources to become comprehensive ambulatory health care centers. It is not known to what extent urban American Indians seek health care from non-Indian providers. Anecdotal findings, based on health-related research in two California cities, indicate that a third of the contemporary urban American Indian population uses non-Indian services, such as employer-sponsored health maintenance organizations. Indian health clinics, however, may be attracting American Indians who have low incomes or are without health insurance.[11]

General Health Profile of Adult Urban American Indians

Data on the health of urban American Indians are extremely limited. Large-scale national surveys, such as the National Health and Nutrition Examination Surveys, do not separate data on urban American Indians from those on the general population. The Indian Health Service does not systematically collect data on diagnostic patient care, vital statistics, or population characteristics for urban American Indians except where this information is included with national-level data on reservation states.[11] The American Indian Health Care Association has recently attempted to collect morbidity and diagnostic data from those urban Indian health clinics that voluntarily record and submit such data; data from five participating clinics are available.[12]

The health profile of American Indians living on reservations is similar to that of the general US population: The leading chronic disease is hypertension, 40% of the population suffers from at least one chronic health condition (cardiovascular disease, cancer, emphysema, gallbladder disease, hypertension, rheumatism, arthritis, or diabetes mellitus), and rates of rheumatism and arthritis are comparable to those of the population at large. American Indians and Native Alaskans, however, are twice as likely to have diabetes mellitus as the general US population and 1.4 times as likely to have gallbladder disease.[13] Both urban clinics and reservation health facilities reported that diabetes and hypertension were among the ten leading diagnoses.[12]

The available research on urban American Indians is generally of smaller scope.[11,14-16] In published studies, the populations surveyed were somewhat homogeneous, and the samples consisted overwhelmingly of persons who reported low socioeconomic status. Therefore, the findings may relate to conditions of poverty at least as much as to ethnicity.

Urban American Indians are at high risk for both cardiovascular disease and diabetes mellitus. A study of health clinics in Oklahoma City, Oklahoma, and Wichita, Kansas, in 1983 and 1984 indicated that approximately half of the clinic visits were to obtain physical examinations or because of diabetes or hypertension for both men (52.04%) and women (48.56%).[11] A study in Minneapolis found health risk patterns consistent with high cardiovascular morbidity and mortality in its finding of high frequencies of obesity, diabetes, and cigarette use and of moderately elevated levels of blood pressure and serum cholesterol.[15] No sex-related differences among risk factors were found for American Indians.

Treating American Indian Patients

No single approach to health care can respond to all the cultural and linguistic variations among American Indians. Furthermore, specific cultural values persist to varying extents for Indians living in an urban area. Typical attitudes of urban American Indian patients toward Western medicine range from indifference by traditionalists, through acceptance by bicultural people who expect scientific medical treatment, to rejection by pantraditionalists seeking to redefine an Indian identity in an urban setting.[17] Despite this variation, some general considerations (although developed, for the most part, to serve more traditional clients) may be of value to orient health care professionals.

American Indians perceive various barriers to obtaining social and health care services. Some of these barriers are based on mutual misinterpretations of cultural norms and etiquette. Elders in particular have encountered blatant racism and also have suffered the pernicious effects of stereotyping. Added to this are their cultural perceptions that many mainstream attitudes are intolerably rude, such as getting right down to business; addressing strangers in loud, confident tones; and frequently interrupting speakers. These attitudes increase social distance and decrease confidence in non-Indian professionals. Older American Indians report that they fear non-Indian health professionals, do not expect to be treated fairly by them, and anticipate adverse contact experiences.[18]

Among urban American Indians, there are two main criteria for selecting a physician: The clinician was either an American Indian—and thus shared unspoken assumptions about health and behaviors based on ethnicity[19]—or a non-Indian who treated the patient with respect and understanding. Therefore, health care professionals should be particularly aware of the need to establish a relationship conducive to treatment.

On a first visit, American Indian patients may test the friendliness and sincerity of a physician. It is not unusual for American Indians to express either passivity or hostility in uncomfortable new situations.[20] American Indian patients may withhold important information until an appropriate atmosphere and trusting relationship have been established. As

Everett Rhoades, director of the Indian Health Service, explains,

> This may require more than one visit and may tax the patience of a busy physician. Even in the face of hostility, a calm, accepting, nonjudgmental manner will almost always be of value.[20(p59)]

A successful therapeutic relationship with an American Indian patient, as with any other patient, requires the physician to establish an interest in the patient's well-being. Significant differences in etiquette between the non-Indian physician and the American Indian patient may inhibit the process, however. For instance, many American Indians expect that the initial visit should begin with the formality of a brief, light handshake, "often little more than a touch."[17,20] This is not the firm business handshake that, while commonplace among non-Indians, is a sign of aggressiveness among American Indians. Further, American Indians consider staring and excessive eye contact not only rude but an invasion of privacy or dignity.[17,20] On the contrary, non-Indians associate eye contact with frankness and equate avoiding eye contact with furtiveness. Responding to a patient's cues on etiquette is one way that health care professionals can avoid misunderstandings.

Until American Indian patients feel comfortable, physicians "should be prepared to be very indirect in asking questions."[20(p59)] Rhoades comments that questions about the use of traditional medicine may be asked directly if the physician uses a nonjudgmental attitude: "Have you been seen by an Indian doctor?" The term "medicine man" should not be used.

Urban American Indian patients may see no conflict between using Western medicine and traditional medicine.[21] Traditional American Indian medicine is holistic and wellness oriented.[17,22,23] It focuses on behaviors and life-styles through which harmony can be achieved in the physical, mental, spiritual, and personal aspects of one's role in the family, community, and environment. Traditional Indian healing practices may substantially reduce patients' stress.

Using the approach of nonjudgmental acceptance, physicians can probe for specific information about the presenting issues and the ways in which an American Indian patient perceives the disease course and treatment. Manson recommends a "mini-ethnography" approach to taking a patient's history—treating illness as distinct from disease, thus recognizing that the patient and physician may have different ways of approaching health (S. M. Manson, "Older Ethnic Minorities and Health Care: Accommodating Cultural Diversity in Clinical Practice," unpublished data, 1992). Illness is a patient's experience of the symptoms, how those symptoms affect the patient and his or her social networks, how those symptoms are understood and responded to, and the complaints brought to the attention of the physician. Disease is the "recasting of illness within a biomedical model," providing the illness with a diagnosis, interpretation, and treatment.

The health care professional can use the mini-ethnography approach to establish an empathic rapport while trying to understand the presenting complaints from the patient's point of view. By asking follow-up questions to the patient's description of the illness and how it affects aspects of everyday life, the physician can gain insight into the patient's world, develop more effective strategies for clinical care, and encourage greater compliance with treatment. Because "American Indian beliefs and attitudes about health and illness are often in direct conflict with the Anglo society,"[17(p251)] using the mini-ethnographic approach can overcome potential cross-cultural misunderstandings. Not only does this approach advance both clinical goals (Manson, unpublished data, 1992) and professional development,[17] but learning about other cultures through this method of inquiry can be a rewarding personal experience.

Urban American Indian Elders

Access to Services

American Indians who migrated to urban centers in the post-World War II era are now reaching retirement age. Of 353 elders in Los Angeles who were asked, 81% reported that they did not plan to return to natal reservations.[24-26] In fact, increasing age is associated with a greater commitment to remain in the city.[27] Some health care[28] and social service[29] professionals, however, erroneously thinking that few older American Indians live in our nation's cities, have either turned away clients or failed to plan services for this population.

Even at middle age, American Indians have been found to suffer physical, emotional, and social impairments characteristic of the general US population aged 65 or older.[30] On reservations persons appeared to be old at 45 years of age, and in urban areas American Indians appeared old by age 55. The greater need for services for the aged has been recognized by the federal government's Administration on Aging, but the age for service eligibility has been lowered only for tribal contractors on reservations. In urban areas, service eligibility is based exclusively on chronologic age.

American Indians are less likely than non-Indians to define aging by chronology. The American Indian community, both on and off reservations, uses social role functioning (for example, grandparenting) and decline in physical activities to define who is considered an elder.[31] In Los Angeles, the median age for both men and women who were considered elders by the community was 58 years.[24]

In urban areas, poverty characterizes the lives of approximately a third of older American Indians, although there are no substantial differences in the labor participation and employment of whites and urban American Indians aged 65 and older.[32] About half of urban American Indians aged 75 or older live with family members. These families are three times as likely as their white counterparts to live in poverty. Generalizations about family support systems must be tempered by the knowledge that, if living in poverty, their resources are scarce and irregular.

Health Profile

Information on urban elders' health was collected in surveys conducted through the auspices of American Indian organizations in Phoenix, Arizona[26]; Los Angeles[24]; and a national multisite survey.[30] Findings are consistent across sites. Although responding with generally positive self-assessments on their health, most elders suffered from one or more health problems at the time of their interview (Table 1).[24,29,30] American Indian elders living in Los Angeles rated health care as their primary concern and top priority for service.[24] Compared with American Indians aged 45 and older living on reservations,[30] the elders in Los Angeles reported higher rates of problems with eyesight (65.9% reported having this problem), hypertension (30.7%), diabetes mellitus (19.8%), asthma (8.1%), stroke (4.9%), speech

TABLE 1.—*Diseases or Specific Symptoms Reported by American Indians Aged 45 and Older*

Health Problem	Los Angeles (n=283), %*	National (n=712), %†	Health Problem	Los Angeles (n=283), %*	National (n=712), %†	Health Problem	Los Angeles (n=283), %*	National (n=712), %†
Eyesight	65.9	54.6	Headaches	11.0	28.5	Speech problems	4.6	1.4
Arthritis/rheumatism	36.4	42.6	Depression	11.0	NA	Prostate	4.0‡	NA
Dental problems	33.2	NA	Stomach problems	10.2	NA	Goiter	3.9	NA
Hypertension	30.7	19.3	Chest pains	8.5	NA	Swallowing	3.9	NA
Joint pains	29.3	NA	Asthma	8.1	4.3	Other ailments	3.9	16.4
Back pains	29.3	NA	Loneliness	7.8	NA	Paralysis	3.5	5.7
Sadness/grieving	22.4	NA	Atherosclerosis	7.4	NA	Trembling	3.5	NA
Hearing problems	21.0	44.4	Skin problems	7.4	NA	Liver problems	3.5	1.6
Foot care problems	20.5	NA	Urinary or bladder problems	7.1	NA	Kidney stones	3.2	8.9
Diabetes mellitus	19.8	12.5	Coughing	6.7	NA	Mental illness	3.2	7.9
Sleep problems	17.0	30.4	Infections	6.2	NA	Amputation	2.8	1.2
Heart problems	14.8	16.1	Osteoporosis	5.7	NA	Elimination problems	2.5	NA
Breathing problems	13.1	34.0	Dizziness	5.7	NA	Cancer	2.5	1.1
Allergies	12.0	NA	Stroke	4.9	3.2	Tuberculosis	2.1	5.0
Swollen ankles	11.3	NA				Gallstones	0.4	NA

NA = not assessed

*From Weibel-Orlando and Kramer[24] and Kramer.[29] †From National Indian Council on Aging.[30] ‡For this item, n = 135.

problems (4.6%), liver problems (3.5%), amputation (2.8%), and cancer (2.5%). Although no comparable data were collected by the National Indian Council on Aging, a high frequency of dental problems was noted in Los Angeles; these were the third most frequently identified health problem.

Although most of the elders living in Los Angeles reported no impairments in either activities of daily living (such as bathing or eating) or instrumental activities of daily living (such as money management or preparing meals), those who were impaired tended to report multiple impairments.[29] The greatest number of impairments and the strongest correlation with age related to instrumental activities of daily living, especially the ability to use a telephone, handle finances independently, and prepare meals. Increasing age was also associated with limitations in activities of daily living, with the strongest correlations found in bathing, transfer, and mobility. The larger sample of American Indian elders residing in Los Angeles reported levels of impairments greater than those reported in the smaller samples collected by the National Indian Council on Aging from several urban sites (Table 2).[29,33]

In Los Angeles nuclear households were common, but frail elderly persons typically lived in multigenerational households.[29] Often unmarried children or grandchildren accepted the role of care giver. Thus, the family support system is an essential component of treatment compliance. Just as health beliefs vary culturally, the expression of care giving may also vary. In contrast to non-Indian family care givers, American Indians may feel less anger and guilt toward dependent elders.[34] The preferred coping strategy is passive forbearance. This is not fatalism but rather an embracing acceptance of the reality of aging relatives.

In most urban areas with large American Indian populations, access to community-based long-term care support services is limited at best.[35] Urban American Indians are typically underserved by the federally funded network of services for the aging.[29] The gap in services is caused by a combination of factors, including allocation of services based on an economy of scale that penalizes small populations, access barriers, and lack of policy initiative. Urban elders were also found to be more disadvantaged than their on-reservation peers in receiving critical information about access to psychological and supportive services from their attending physicians.[36]

Prospects for Health Care

The number of American Indians living to old age (65 years or older) is increasing. The elderly comprise the fastest-growing segment of the US population,[37] and the number of American Indian elders is projected to double by the year 2000.[38,39] Increasingly this older population, with its high burden of chronic diseases, will be coming to the attention of physicians in a variety of settings.

TABLE 2.—*Impairments in Functional Status Reported by American Indians Aged 45 and Older*

Impaired Activity	Los Angeles (n=294), %*	Other Urban Areas (n=96), %†‡
Activities of daily living		
Bathing	7.7	4.2
Dressing	5.9	2.2
Toileting	4.9	NA
Transfer	8.1	1.1
Feeding	2.4	2.1
Mobility	13.1	7.4
Instrumental activities of daily living		
Telephone	5.4	7.4
Finances	7.2	2.2
Shopping	19.0	11.9
Transportation	19.2	10.8
Meals	15.2	5.4
Housework	19.7	20.4

NA = not assessed

*From Kramer.[29]
†The sample population was surveyed by the National Indian Council on Aging in the following cities: Pittsburgh, Pa; Tulsa, Okla; Denver, Colo; Minneapolis, Minn; and Tacoma, Wash.
‡From American Indian Health Care Association.[33]

American Indians living in urban environments face the same health care dilemma as other Americans.[40] Those lacking adequate health insurance and financial resources will find the availability of health care services limited by their ability to pay. Poverty and cultural patterns contribute to the

vulnerability of many urban American Indian elders. These elders are usually unwilling to "endure the gauntlet of waiting rooms and clinics" and find welfare clinics a humiliating experience, one to be avoided.[28,41] Elders are not adept at cutting through "white tape." The high costs of health care and medication make these items a low priority for those living at poverty level.[42] Elders have the lifelong experience of being turned away from public clinics whose staff incorrectly insist that the Indian Health Service is the sole agency responsible for their care.[28,43] In recent years, the Social Security Administration has targeted outreach projects to assist ethnic minorities to receive supplemental income assistance. It is hoped that greater access to Social Security, Medicare, and Medicaid will also improve access to adequate health care.

Summary

Although little has been reported about urban American Indian populations, the sparse literature suggests a population at risk, especially for cardiovascular disease and diabetes. The number of American Indians living in cities has increased dramatically since World War II, and currently more than half of the total American Indian population lives in our nation's cities and towns. Urban American Indians use a variety of health care settings, although most studies have concentrated on clinics serving a low-income clientele. An increasing number of older urban American Indians, typically with high rates of chronic diseases, will be seeking medical care in urban areas in the coming years. Social, cultural, and economic barriers continue to impede access to health care services. Health care professionals can take an active role in reducing the perceived barriers when treating American Indian patients.

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- African Americans make up 12% of the US population but 30% of all diagnosed AIDS cases
- Homosexual men are a declining proportion of African Americans with AIDS; drug injecters and women are an increasing proportion

AFRICAN AMERICANS

Cross-cultural Medicine
A Decade Later

African-American Culture and AIDS Prevention
From Barrier to Ally

BENJAMIN P. BOWSER, PhD, *Hayward, California*

African Americans make up an increasing proportion of persons with the acquired immunodeficiency syndrome (AIDS). I identify and describe cultural elements such as oral traditions, multiple naming, a collective identity, extended families, and sexuality influenced by myth and exaggeration that condition African Americans' reactions to AIDS prevention. I also offer suggestions on how these cultural elements can be used for effective AIDS prevention efforts in African-American communities.

(Bowser BP: African-American culture and AIDS prevention—From barrier to ally, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:286-289)

African Americans are 12% of the United States population but are 29.6% of all diagnosed cases of the acquired immunodeficiency syndrome (AIDS). This proportional disparity is increasing each year, driven primarily by human immunodeficiency virus (HIV) infections among male drug injectors and their female sexual partners. African-American gay and bisexual men are a declining proportion of African Americans with AIDS.[1] In addition, there is a strong likelihood of a third cluster of HIV infection among economically disadvantaged and socially isolated African-American adolescents. Many of these teens are sexually active, have social networks intertwined with drug injectors, and have persons in their sexual networks engaging in sex for drugs as part of the crack cocaine subculture.[2]

Although the rising threat of AIDS is undeniable among African Americans, there has been no general mobilization among African-American communities for AIDS prevention, despite universal awareness of the disease.[3] African-American gay and bisexual men and drug injectors have made some progress in reducing their sexual and needle-sharing risks, but sexual HIV risk taking is still common within the heterosexual noninjecting majority.[4(p160)] Poverty and social isolation are major barriers to effective AIDS prevention but so also are African-American attitudes toward sexuality. Culture as well as circumstances influence sexuality.[5] If known and used, culture can be an ally in AIDS prevention efforts.

African Influence on African-American Culture

Elements of the African worldview survived slavery in the Americas. Africans taken as slaves were drawn from mixed cultural backgrounds with varied sexual practices that ranged from examining young women for virginity at marriage to the condoning of sexual contact and childbirth before marriage.[7] African cultural influences were reinterpreted into Western customs and then reinforced and sustained in the past century by racial segregation.[6] Despite different sexual practices in West Africa cultures, spiritual concepts were similar. The physical world was viewed as part of a larger cosmology. One's spirit was not, as in the European cosmology, a separate and individual soul with an individual fate. Rather, each spirit, though personal and unique, was part of a larger collective spirit and shared in a collective fate. Living persons were part of a continuum of spirits with ancestors at one end and spirits yet to be born at the other. Sexuality was defined within this spiritual context.

Past and future spirits are not imagined.[8] They are real, have personalities, and can be communicated with. For example, in the United States South, it is not unusual for African-American old people to talk with deceased relatives and to have spirits pass on important information to them in dreams. For people immersed in an African cosmology, communicating with spirits is normal, expected, and necessary. Boundaries between the spirit world and the physical plane are not rigid. "Being" is based not just on thought and empirical and physical evidence but is spiritual and collective. This African worldview has been a unique source of strength African people have drawn on to survive slavery and racism and is clearly evident in African-American churches. The "saved" literally have personal relations and encounters with the saints, ancestors, and "The Holy Ghost." Religion is not contemplative and idealized. It is active, present, and to be experienced directly. Individual church members have life missions to achieve and paths to follow, as does the entire congregation.

Black participation in this African-American culture ranges across a continuum from those who have little knowledge, experience, or identification with the African-American subculture to those reared and socialized in African-American culturally specific families and communi-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

ties.[9] Most African Americans are at neither extreme and are essentially bicultural. Historically, the African-American cultural continuum has roughly overlapped social class divisions. The lower and working classes have been the maintainers of "the roots," and the middle class has been more European oriented.

African-American Culture and AIDS Prevention

Social class circumstances condition when, if, and how African-American culture determines the context of behavior. Of particular interest is how the culture informs lower and working-class African Americans' reactions to AIDS prevention efforts. The following are brief reviews of social class-specific and other selected aspects of the African-American subculture, with a discussion of their relevance to AIDS prevention.

Oral Tradition and Multiple Naming

Participants in the African-American subculture engage in a highly sophisticated oral tradition.[10] Slaves could not keep written records, so continuing African oral practices became vital to maintaining a sense of community. Information was not simply passed from person to person; then, as today, information was orally critiqued, spoken for, and challenged. People in an oral network ask, "How do you know that's right?" "Who told you?" "Do you believe that?" "So-and-so said it [implying that it must be right or wrong]." What is passed and accepted verbally is believed. Written material does not have the credibility that it has in the mainstream culture. Oral networks are the pulse of the community and the conduits for what people are thinking.

Closely related to the oral tradition is the use of multiple names.[11] A person will have one name that is used in public—for police, social service agencies, or for people "from downtown." That person will also have a family name, a street name, and a name among friends. This is much more than the American custom of nicknaming. It originates in the African belief that names have powers, resonate with particular spirits, indicate membership and acceptance, and give the persons who hold them certain abilities. In the African-American lower class, when a stranger addresses someone by one of his or her names, the name the stranger uses tells immediately who that person is, where that person is from, and what type of business he or she wishes to conduct.

Oral traditions and multiple naming have direct implications for AIDS prevention because of the ways they can bias any household survey. This is evident when attempts are made to interview a black person who has multiple names by asking for that person by his or her official name. Respondents can self-select themselves out of a sample without directly declining to be interviewed. A person with any reason for not wanting to talk with "the man" will not be home, will have just moved, or will take a message. Successful surveys must reach urban lower-class African Americans from within their own social networks, and this can be accomplished by people who they know and have some basis for trusting. If AIDS information—in particular the "safer sex" message—is passed on orally by a known and trusted person in the network, it then has the possibility of being believable and meaningful. If this information is not transmitted by the right person or not accepted by the oral networks, it will be resisted, mistrusted, and considered just another attempt by whites to tell blacks how they should live.

Collective Identity

If someone has a worldview with a collective sense of spirituality, then a wide range of positive social relations becomes essential to that person's sense of self, personal well-being, and community. Ideally, a person should have close, emotionally supportive, and trusting relations extending well beyond family and immediate friends. Most African Americans are deeply embedded in an affirming community and a collective in which they are acknowledged and nurtured. Personal property is readily assumed to be shared with others, and collective efforts are valued more than individual efforts. Family titles used to address nonkin and to refer to the collective—"Sisters" or "Brothers"—further emphasize the collectivity. This strong sense of the collective makes alienation from family, friends, or community all the more painful as happens among AIDS and HIV-positive persons.

Collective identity also has direct implications for AIDS prevention. First, convincing people to change their behavior can be effective in this collective context. Attempting to change a group by changing each member goes against the culture. Second, agents of change will have to come from within all of the organizations and communities that make up the African-American collective. Finally, if AIDS and AIDS sufferers are viewed as being outside the collective, as they have been until recently, then messages about AIDS prevention will be ignored.

The Extended Family

The high prevalence of female-headed households, teen pregnancy, and high divorce and separation rates seem to affirm the notion that African Americans do not place a high value on family. Quite the opposite is true. African-American culture is strongly family centered. Family is more broadly defined as extended relationships, and variations from the white middle-class—that is, nuclear family—are tolerated. African-American families are organized around blood lineages where the oldest members are the heads of an extended family.[12] The family is rooted primarily in the father's or mother's lineage and only secondarily in a particular nuclear household. In addition, persons who have assisted or been of value to the family are accepted as family members and given titles, such as "Aunt" or "Uncle," "Brother" or "Sister."

Extended families are helping and exchange networks that engage in mutual support, collectively rear children, and provide emotional support across the generations.[13] If a mother or father is missing, then an aunt, uncle, older brother or sister, or grandparent will step into that role. The primary socialization of each family member occurs as part of their extended family's age cohort.

With regard to AIDS prevention, the extended family has great untapped potential. If the family head acknowledges the AIDS threat, then AIDS prevention information is given more credence, and family members at high risk are more likely to give it attention. Many of those who continue to engage in high-risk behaviors are no longer part of an extended family. A powerful way to have an effect on these people is to involve them in surrogate extended "families" with AIDS prevention as one of the group's goals.

Sexuality

Commonly cited aspects of African-American sexuality are early and more frequent coitus, infrequent use of condoms, high rates of teen pregnancy, and the male double standard.[14] Although these behaviors are undoubtedly influenced by history and culture, there is no evidence that they are highly regarded or idealized in any class of African Americans.[15]

It is ironic that we may know more about African-American sexuality during slavery than now. Since 1966 studies of black sexuality have consisted mostly of comparisons of white and black sexual behaviors with a primary focus on African-American lower-class adolescent girls' behavior. The most popular samples are from family planning clinics.[16] The few studies to examine the African-American middle class have found earlier and slightly more sexual activity than in their white counterparts.[17] Historically, however, the black and white middle classes were not directly comparable. African-American middle-class sexuality continues to be closer in attitudes and values to the white working class.[18(pp116-132)] What is African-American sexuality apart from more frequent intercourse and earlier sexual activity?

The average age of marriage, rate of divorce, and extent to which children are born to a single parent have been conditioned by the availability or absence of jobs and how well they pay. When there are jobs and decent wages, the age of marriage and divorce rates drop and the number of "illegitimate" births declines. Maintaining a nuclear family unit is heavily dependent on participation in the urban wage economy. It is virtually impossible for persons at the edge of or outside the economy to form or maintain a nuclear, two-parent household.[19] In contrast, compared with lower-class black sexuality, the African-American middle class has moved to the opposite extreme.[20] That is, sexuality is not allowed to compromise a person's economic and social class status. There is no general acceptance of sexuality, especially among middle-class women. Besides economic influences on African-American sexuality, there are three cultural factors related to reproduction and gender that are special barriers to effective AIDS prevention.

Myths That Distort African-American Sexuality

In the African-American lower and working class, sexuality is not conditioned by centuries of religious and moral denial. Positive African-American lower-class values toward sexuality are not barriers to AIDS prevention, but three values are. The first is that children are an affirmation of manhood and womanhood and the basis for claiming status as adults.[21] This value is the basis for the reluctance to use condoms. The second factor is the myth of black sexual superiority. The perceptions of white and black sexuality in the United States are heavily conditioned by the racist presumption of white superiority and black inferiority.[22] Axiomatic to this racist ideation is that African Americans are sexually superior to whites. The problem with the myth of black sexual superiority is that it has carried over into the nation's conventional wisdom. The African-American lower class's positive attitudes toward sex play into the myth, reinforcing it, and providing ample evidence of its alleged validity. A more serious problem is that many African Americans believe the myth as well. The black male double standard and the need to affirm manhood and womanhood through the production of children are then reinforced by the need to demonstrate and affirm alleged sexual superiority.

The third factor that distorts African-American sexuality is the propensity of giving words multiple meanings and exaggeration. In African traditional societies, there were "praise-sayers" whose purpose was to repeat the great deeds of a leader or a people or to commemorate a special occasion. Praise-sayers prepare for a great presence or occasion that is intended to be larger than life. Exaggeration and word play are very much a part of contemporary African-American culture. In both public and personal social encounters, sexual activity is not only a topic of discussion, it is often talked about loudly in bold, colorful, and exaggerated language. Real and imagined behaviors are all one. A speaker may grossly exaggerate or say something meant to be shocking to challenge listeners to say something even bolder. This is a form of entertainment, and community members who are skilled at it are held in high regard. Listeners and interviewers who are unfamiliar with the culture are especially looked on as fair game for entertainment through exaggeration about sexual experiences. This propensity to exaggerate sexual exploits can lead to pitfalls for unwary sex researchers.

Culturally Specific AIDS Prevention

African-American community institutions—churches, families, organizations—have yet to be mobilized for greater efforts toward AIDS prevention. Black culture can be used as a resource and a powerful force encouraging HIV–low-risk behaviors among working and lower-class African Americans. The way to use African-American culture as a positive force in preventing AIDS rather than have it continue as an insurmountable barrier is first to recognize the unique elements of the culture and to use those elements to advantage. There are a number of ways to go about this:

- Information about AIDS prevention among African Americans will have to come from within the community and from people familiar with the culture. Those who are familiar and are accepted can get around multiple identities, have access to the oral networks, and can recognize and counter oral exaggeration.
- The most culturally effective mode of AIDS prevention among African Americans would be consistent and repeated person-to-person and person-to-group oral discussion. Through question and answer, challenge and discussion, people can be convinced of the risk of contracting HIV and of the effectiveness of low-risk behaviors.
- The African-American sense of a collective identity has the potential to develop a strong norm for low-risk HIV-related behaviors. This will develop once AIDS is seen as a real risk to the community.
- The extended family is the most powerful untapped tool in preventing AIDS in African Americans. An effective strategy could be to train the heads of extended families to be AIDS educators and counselors to work within their families and their neighborhoods.
- African-American sexuality does not need to undergo wholesale revision to meet the AIDS challenge. Specific change is needed in the use of sexuality as a way to affirm adult status and manhood or womanhood by having children. The belief among African Americans in black sexual superiority will have to be recognized for what it is—a myth that leads persons to engage in risky behavior.

I have described selective elements of African-American culture. These elements are some of the reinterpretations of original African cultures that have enabled Africans to survive slavery, become African Americans, create communities, and resist racial subordination. These cultural elements can be the basis of successful communitywide AIDS prevention programs. Arising from the needs for survival and resistance, this formidable culture has yet to be mobilized effectively to halt the growing threat of AIDS. If such a mobilization is to be effective against AIDS, it must come from within a community struggling with high unemployment, school-dropout rates, and drug sales and use. The timing and effectiveness of this mobilization is going to depend on African Americans making leaders and institutions more accountable to the needs of its growing underclass. This does not mean that African Americans are the only ones who can prevent AIDS in their community, nor does it mean that the white community engaged in prevention should remain "downtown" and control these efforts in African-American communities through designates. Mobilization against AIDS is going to also depend on the preventive health community's willingness to recognize this complex culture, provide resources, and allow indigenous leaders to develop and refine strategies for AIDS prevention in their communities. Only in this way will the people who need it most be reached and convinced to make the needed changes.

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- Since 1975, over 700,000 Vietnamese have resettled in the United States
- Initial immigrants were an educated, wealthy elite; by 1978, a second wave of poorer refugees from a more mixed occupational, economic, and regional class were leaving Vietnam by boat

Cross-cultural Medicine
A Decade Later

Mental Health and Illness in Vietnamese Refugees

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Despite their impressive progress in adapting to American life, many Vietnamese still suffer from wartime experiences, culture shock, the loss of loved ones, and economic hardship. Although this trauma creates substantial mental health needs, culture, experience, and the complexity of the American resettlement system often block obtaining assistance. Vietnamese mental health needs are best understood in terms of the family unit, which is extended, collectivistic, and patriarchal. Many refugees suffer from broken family status. They also experience role reversals wherein the increased social and economic power of women and children (versus men and adults) disrupts the traditional family ethos. Finally, cultural conflicts often make communication between practitioners and clients difficult and obscure central issues in mental health treatment. Rather than treating symptoms alone, mental health workers should acknowledge the cultural, familial, and historical context of Vietnamese refugees.

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A recently arrived Vietnamese woman who believed she was taken over by a ghost was brought by family members to the Community Mental Health Agency. Our staff was unable to help her. After a period of time, she asked us to take her to a Buddhist Temple. We did. She was exorcised and prayed over. After that, she was fine.

In retrospect, we have many questions. What really happened? Is this an appropriate modality of treatment? Can we bridge between the client and an outside source of assistance or are we legitimizing a method of treatment that is totally unscientific but may work?

INCIDENT REPORTED BY MEDICAL SOCIAL WORKER IN SAN FRANCISCO, CALIFORNIA

More than 700,000 Vietnamese currently live in the United States. By century's end, they will be the third largest Asian-American group.[1] They are a socially diverse population whose members range from Western-educated professionals to rural peasants. Although the Vietnamese have made impressive progress in adjusting to life in the United States, many still suffer from various difficulties rooted in wartime experiences, their flight from home, culture shock, racial prejudice, the loss of and separation from loved ones, and economic hardship. As indicated in the epigraph, addressing these issues offers unique challenges for mental health professionals. In this article I outline the resettlement experience of Vietnamese refugees and describe their efforts to obtain mental health services in the United States.

Flight and Adjustment for Three Subgroups

The Vietnamese refugee population is made up of three distinct subgroups—the first-wave elite, the boat people, and the ethnic Chinese. These three groups share a common experience as refugees, with similar cultural values and frequent interaction, but they also retain many social and cultural differences and have developed fairly disparate patterns of adaptation to the United States. Accordingly, their mental health needs and ways of relating to professional helpers are frequently distinct.

The first group of Vietnamese refugees entered the United States between 1975 and 1977. As former US employees and members of the South Vietnamese military and government elite, many arrived with families intact. Their links to Western culture are indicated by their high levels of formal education and the fact that almost half were Catholic, even though more than 80% of all Vietnamese are Buddhists.[2,3] Drawing on their skills, education, competence in English, familiarity with Western culture, and extended families, many adjusted rapidly. By the mid-1980s, the Office of Refugee Resettlement reported that the average income of first-wave refugees matched that of the larger US population.[4]

The second wave of Vietnamese refugees—commonly called the boat people—began to enter the United States after the outbreak of the Vietnam-China conflict of 1978. Generally hailing from more plebeian origins and characterized by less education and lower levels of English competence than the first wave, these refugees lived for three or more years under Communism, sometimes laboring in re-education camps or remote "new economic zones" before leaving Vietnam. Their exit, involving clandestine escapes and open-sea voyages in leaky, overcrowded boats or long journeys on foot across revolution-torn Cambodia to Thailand, was subject to attack by pirates and military forces. Reportedly as many as half of those who attempted such an escape from Vietnam

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perished in flight. Those lucky enough to survive spent several months in the overcrowded refugee camps of Thailand, Malaysia, Indonesia, the Philippines, or Hong Kong before entering the United States.[5]

Owing to the dangers of escape, far more young men than women, children, or older people left Vietnam as boat people, yielding broken families and imbalanced sex ratios.[6] The boat people had more severe troubles in adapting economically than earlier arriving Vietnamese—including high levels of unemployment and welfare dependency (64%) and low rates of labor force participation (37%, more than 1½ times the national average). Thousands continue to live below the poverty level (Table 1).[7,8]

Within the second cohort of Vietnamese refugees, a sizable subpopulation exists. This group comprises members of Vietnam's ethnic Chinese minority, most of whom arrived after 1978 as boat people. Constituting an entrepreneurial class, these refugees frequently create Chinese-Vietnamese organizations and businesses in the United States. Because of ethnic differences and economic conflicts with the ethnic Vietnamese, relations between Chinese-Vietnamese and ethnic Vietnamese were often strained in the country of origin, and many of these conflicts continue in the US.[10,11]

TABLE 1.—*Characteristics of Vietnomese Refugees in the United States: First Wove ond Boot People**

Characteristic	Vietnamese Refugees: First Wave (1975-1977)	Vietnamese Refugees: Boat People (1978 and after)
Average years of education	9.5	7.05
No English on arrival, %	30.6	50
Age		
% <36 yr	30.6	58
% >56 yr	10	5
White collar occupation in Vietnam, %	78.7	49.2
1980 Household income		
<$9,000, %	27.6	61
>$21,000, %	31	4.6

*From Office of Refugee Resettlement7 and Nguyen and Henkin.9

Because few Chinese-Vietnamese have a Western education, they seldom work as high-level professionals, such as resettlement workers or Western health care professionals. Many are practitioners of Chinese traditional medicine, however. The existing network of refugee professionals and agencies that provides services to the refugee community is staffed by the ethnic Vietnamese, a group that many Chinese-Vietnamese consider hostile, making them reluctant to use such services. Health care professionals need to be aware of such interethnic conflicts when dealing with clients and supervising refugee staff.[8,12,13]

Family Issues Among Recently Arrived Vietnamese

The traditional Vietnamese family is perhaps the most basic, enduring, and self-consciously acknowledged form of national culture among refugees. It is customarily a large, patriarchal, and extended unit including minor children, married sons, daughters-in-law, unmarried grown daughters, and grandchildren under the same roof. Individualism is discouraged, whereas collective obligations and decision making are emphasized.[3,14] The traditional family has been altered as a consequence of Western influence, urbanization, and the war-induced absence of men. Nevertheless, many Vietnamese continue to uphold this social form as the preferable basis of social organization in the United States.

Positive adaptation is often facilitated through family-based cooperation.[15-19] Because of wartime casualties and tenuous conditions of escape, however, many Vietnamese refugees must contend with broken families in the US. This, combined with cultural factors, such as the American emphasis on nuclear families, makes family adjustment traumatic for many Vietnamese. Prizing family connections, groups of recently arrived unattached male refugees create "pseudofamilies"—households made up of close and distant relatives and friends.[20] Sharing accommodations, finances, and fellowship, these collectives form an important source of social support in the refugee community. Although refugees find some comfort in household networks, their ability to establish regular families is often limited by poor economic status and the scarcity of Vietnamese women in the United States.[21,22]

Role Reversals

Vietnamese refugees of all subgroups have various degrees of reversal of the "provider" and "recipient" roles that existed among family members in Vietnam.[23] A common shift of roles occurs between husband and wife, with the wife taking on the breadwinner role and some of the status and power that accompany it. This is because women's jobs—hotel maid, sewing machine operator, and food service worker—are more readily available than the male-oriented unskilled occupations that the husband seeks. In other cases the wife becomes the breadwinner and supports the family by working in a menial job while the husband attempts to find professional employment. Finally, some women have to assume breadwinner roles because of the absence of a spouse in the US. Role changes also occur in families where both the husband and wife work because the wife was generally not employed outside the home before the family came to this country.

Role reversals between parents and children are also common because children often learn the English language and American customs rapidly and may be able to find employment more quickly than older members of the family. Such role reversals often yield generational conflicts within refugee families in which the traditional culture is collectivistic and emphasizes the deferential treatment of elders, whereas American society is individualistic and youth oriented.[24] For young refugees, the pressure to conform simultaneously to American and Vietnamese cultures—which are in many ways incompatible—is a major source of strain.

Since the late 1980s, thousands of survivors of re-education camps, mostly former government and military officials and nearly all ethnic Vietnamese men, have been permitted to leave Vietnam and join their families who are already well established in the United States. These families are especially susceptible to traumatic role reversals and other family troubles because of the long period of separation. Further, although the husband may wish to retake his role as breadwinner and patriarch, he is ill-equipped to accomplish this task because he is unaccustomed to American society and must overcome the effects of years of incarceration.[25]

The process by which women or children rather than men become the primary source of refugee family income indicates the adaptability of Vietnamese families. At the same

time, however, the inversion of traditional family roles often provokes hostility and resentment. Social workers with refugee clients comment that self-destructive, violent, psychosomatic, or antisocial reactions—such as wife or child abuse, depression, or alcoholism—occur as a result of family role reversals.[26-29] Role reversals are especially traumatic for the Chinese-Vietnamese because they often maintain more traditional family patterns than the ethnic Vietnamese.[30]

Media reports and academic research reveal—and often overemphasize—the bipolar adaptation of Vietnamese youth. One group, most often children of first-wave refugees, are "academic superstars," graduating first in their class at many top schools and colleges including the US Naval Academy.[19,29] At the other end of the social spectrum is the involvement of Vietnamese youth in various criminal and gang activities, which are often directed toward other Asian immigrants.[31] Although these two groups illustrate the diversity of Vietnamese adaptation, most refugee youth fall somewhere between the sensationalized polarities of superachiever and delinquent.

Refugee Resettlement System

Vietnamese refugees in the United States must weave through a complex maze of agencies to address the social, economic, and adjustment problems they experience. In so doing they find that their indigenous approaches to problem solving, authority relations, and helping relationships are different from the outlooks maintained by the institutions and staff of the resettlement system.[32,33]

Resettlement and refugee-aid services are delivered and administered by a diverse network of government, religious, nonprofit, and profit-making agencies and organizations. For example, in 1983, there were over 40 agencies resettling Vietnamese refugees in San Francisco alone, with 15 or more in surrounding counties.[34] The large number of resettlement agencies providing service to Vietnamese refugees was inefficient in terms of coordination and allocation of funding and sometimes created interagency competition and hostility.[35-37]

A major role in the resettlement of refugees is carried out by 13 voluntary agencies funded by the federal government.[38] These agencies are decentralized, often overlapping, have few professional staff, and are subject to severe fiscal problems. They generally provide only short-term and survival-type aid. Because most are directed specifically toward the problems of Southeast Asian refugees, few existed before 1975. Further, after the peak of migration in the early 1980s, many agencies had heavy cutbacks in staff and funding or were phased out altogether.

Refugees have a hard time locating agencies that are capable of helping them. A Washington State study revealed that between 50% and 70% of refugees did not know how to obtain vital services such as legal help, free emergency medical care, English classes, free emergency food, or low-income housing that were available to them.[39] Refugees who do use services tend to be among the elite of the community—the 1975 cohort.[40] Refugee clients generally find word-of-mouth referrals from trusted peers to be the most useful source of information about helping agencies.

Interactions With Treatment Staff

Interactions with agency staff and helping professionals frequently take place in an environment of distorted communication and cultural incompatibility.[41] These misunderstandings become painfully apparent when refugees seek mental health assistance. Health assessments show that refugees suffer from various mental health problems that are far more severe than those of voluntary immigrants and the native born.[42] Those most frequently reported are major depressive disorders, schizophrenia, and anxiety and other neurotic conditions.[24,43-45] Vietnamese refugees also suffer from medical problems. Consequently, federal, state, and local governments have funded a number of mental health programs for this population.[46,47]

Unfortunately, most Vietnamese lack the cultural prerequisites of a successful American-style therapy interaction, such as a willingness to confide, a belief in the unconscious, and the ability to criticize parents openly. They have limited familiarity with the treatment of chronic health problems and regard Western medication with a combination of awe and fear. There is no equivalent word in the Vietnamese language for the term "counselor." Mental health problems are so highly stigmatized by the Vietnamese that it is difficult even to discuss these issues without provoking feelings of shame. For example, even highly educated long-established refugees use the terms "mental health" and "mental illness" interchangeably.[48] Most refugees do not see a connection between the process of therapy and the problems that for them are most pressing.[49,50] According to Kinzie, "Many Southeast Asians have an unwillingness or an inability to differentiate between psychological, physiological, and supernatural causes of illness."[43(p116)]

Finally, because of their experience as refugees, Vietnamese do not easily trust authority figures, including treatment staff. Accordingly, refugees often avoid seeking help until the situation is intolerable, and when they do, cooperative relations between helpers and clients are extremely difficult to establish. A Vietnam-born American-educated director of a refugee mental health program described his relations with clients as follows: "For an average Vietnamese, mental health would immediately mean that the person is crazy, acting crazy, saying crazy things."

As a consequence of refugees' difficulties in gaining access to helping agencies and because of their general reluctance to contact professionals to resolve mental health problems, few Vietnamese clients voluntarily seek mental health assistance. Most are referred to service providers by schools, the criminal justice system, and other agencies. Those who willingly seek professional help have often reached a level of desperation. Self-referred clients are generally one of two types. The first type contacts the agency not because of emotional problems but because of practical difficulties, which are often financial in nature—lack of basic necessities such as food, housing, a job, and child care—and the client has no other resource. This type of client comes to the agency out of desperation. Survival problems have become more common recently because of bad economic times and cutbacks in social service programs. Because of confusion in culture and communication, however, discovering the fact that clients' needs, however serious, are rooted in environmental rather than psychiatric difficulties often takes considerable time and effort, even with Vietnamese-speaking staff.

The second category of self-referred clients are those who are having acute mental health difficulties that family members or the affected person can no longer manage. As Muecke has noted,

Disturbed persons are usually harbored within their family unless they become destructive, at which point they may be admitted to hospital . . . or otherwise restrained, but at the great cost of bringing shame to the family.[51(p34)]

Through mutual misunderstandings, helping professionals and refugee clients often unwittingly engage in a "conspiracy of silence" that prevents direct confrontation of the problems at hand. This is further exacerbated by both parties' attempts to avoid embarrassment. Treatment staff resist asking specific questions about mental health problems, and refugees fail to volunteer relevant information. After finally identifying the source of a problem, a physician will state, "Why didn't you tell me?" to which the patient replies, "You didn't ask me."

Practical Suggestions for Clinicians

Practitioners familiar with Vietnamese clients recommend a variety of strategies for addressing the problems of Vietnamese refugee clients. The most general theme might be called a global approach. To untangle the nature of the clients' problems, clinicians need to know about their personal histories, including life in Vietnam, the experience of flight, stay in the refugee camp, and the nature of their current circumstances in the US, such as family, job, and health status.[43,48,52,53] Because refugees may suffer from physical health problems and frequently somatize mental health issues, treatment staff should have access to clients' medical evaluations.[43]

Because refugees are embarrassed by mental health concerns, practitioners should approach such matters in a straightforward manner. This can be fostered by obtaining background information about patients. When mentioned strategically, such information encourages clients to abandon their efforts to maintain a false front that "everything is okay."[45] For similar reasons treatment staff are encouraged to ask their patients direct and specific questions about symptoms. The general question, "How do you feel?" as asked by American physicians is all but meaningless to Vietnamese patients. Instead, the question should be, "How do you hurt?" or "Where does it hurt?"

Treatment staff need to be able to distinguish between mental health problems shaped by culture and those caused by life experiences. For example, although culturally sensitive mental health workers often assume that Vietnamese patients suffer from depression, passivity, interpersonal problems, somatization, and unemployment because of culture shock and the effects of "the Asian worldview," these symptoms may actually have their origins in war-induced posttraumatic stress disorder, a syndrome common to American Vietnam veterans.[52]

As refugees, many Vietnamese have adopted a survival-oriented approach to life. They are more likely to perceive physical symptoms and concrete needs as crucial sources of difficulty. Emotional or psychological problems are seen as less serious or immediate. Although this often serves as an obstacle to treatment, it is also a possible source of strength. Helpers are encouraged to remind refugee clients of their abilities used to overcome past personal challenges and to rely on these coping abilities to resolve contemporary concerns. Selective inclusion of past experiences is also suggested as an important element in therapy so that clients do not ignore traumatic experiences, dwell excessively on painful incidents, or long nostalgically for an idealized past.[28,54]

As a means of dealing with the stigma of mental health problems, Vietnamese refugees often indicate their symptoms by referring to physical problems. In helping refugees deal with physical and concrete matters, however, treatment staff can establish the trusting relations that are essential for addressing submerged psychological issues. Further, although Vietnamese are unfamiliar with the role of a mental health counselor or psychotherapist, their cultural experience is compatible with that of the physician-patient relationship and sick role. Hence, psychiatrists are encouraged to consider prescribing medication to relieve symptoms. Accustomed to traditional Asian herbal medicine, refugees endow Western medications with mythic power. Such treatments impress refugees, but care providers nevertheless report noncompliance, with clients reducing or forgoing doses because of the cessation of symptoms, the occurrence of side effects, or the advice of family members. Blood tests are warranted to assess patient compliance.[43]

In helping refugees deal with adapting to the American culture, the bicultural approach is generally most appropriate. Refugees who have connections with indigenous traditions and coethnic communities as well as the cultural and linguistic skills required for interacting with the larger society appear to achieve the highest levels of economic progress and emotional well-being.[30,55,56]

Finally, because of the central role of the family in Vietnamese life, health workers should understand that they are not only treating a person, but are also indirectly interacting with a group of kin. Treatment staff are advised to enlist the cooperation and trust of the family unit to avoid competitive relations with relatives that may become an obstacle to effective treatment. Because of patients' extensive involvement with their families, mental health professionals need to practice discretion rather than confidentiality in their interactions with family members.[48]

Conclusions

Vietnamese are a socially diverse group. Although their traumatic flight from home and resettlement in the United States often result in substantial mental health needs, their culture and experience make them wary of interactions with mental health workers.

To interact effectively with Vietnamese refugees, mental health workers need to approach them in a holistic manner—understanding that their needs are shaped by their experience as refugees, their economic status, and their unique familial and cultural background. Treatment staff are likely to achieve more satisfactory results if they relate to Vietnamese clients in terms of this complex than if they attempt to treat isolated symptoms.

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Cross-cultural Medicine
A Decade Later

- An estimated 800,000 Iranians have migrated to the United States since 1980
- Most refugees were fleeing the consequences of the 1979 Islamic revolution and the 1980s Iran-Iraq War
- Iranians are a heterogeneous population—socially, religiously, and economically

Dysphoria and Somatization in Iranian Culture

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Iranians express dysphoria through an undifferentiated term called *nārāhati*, meaning depressed, ill at ease, nervous, inconvenienced, or anxious. People try masking this emotion or express it in specific ways nonverbally, such as sulking or not eating. Two other dysphoric affects, sadness and anger, are not masked. Because of the social conception of persons being emotionally sensitive, the expression of *nārāhati* is guarded: expressing it not only could show that one is socially vulnerable, it could also make another sensitive empathic person *nārāhat*. The body is also sensitive, but to the physical world. Physical health is maintained by balancing a diet of "hot" and "cold" foods and avoiding exposure to cold and moisture. With the social and cultural problems brought on by revolution, war, immigration, and accommodation to a new society, Iranian refugees experience changes in family, role, status, finances, language, and other sociocultural ways of being that cause them to feel *nārāhat* and to express it verbally, nonverbally, or through somatization. Understanding Iranian conceptions of emotional and physical sensitivity will help clinicians in treating Iranian patients.

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As a consequence of Khomeini's Islamic revolution in 1979 and later on the Iran-Iraq war, many Iranians immigrated to the United States. These refugees are socially, religiously, and economically diverse. They come from various cities in Iran, each with its own regional subculture. Among the refugees are university-educated middle-class physicians, pharmacists, nurses, engineers, professors, and lawyers, as well as grammar school-educated millionaires, merchants, and artisans. Some were able to bring money out of Iran and start businesses in the United States, whereas others lost their resources. Many families immigrated as a unit, but others split up because siblings, children, or parents were denied passports by the Iranian government. Some Iranians left their country legally by plane, and others escaped overland to Turkey or Pakistan with the help of Kurdish or Bakhtīarī smugglers. Among this latter group were teenagers and young single men avoiding the war with Iraq and young single women escaping the restrictions imposed on them by the Islamic regime. The Iranians in the United States represent the various religions that make up Iranian society: religious and secular Shi'a Muslims, Sunni Muslims, Jews, Christians (Armenians and Nestorians), Bahais, and Zoroastrians.

These social divisions among the Iranian refugees are tempered by a common history, culture, and language and by the similarities of experience wrought by revolution, war, immigration, and resettlement, all of which need to be taken into consideration by health care professionals treating Iranians. The experiences of revolution and becoming refugees often affect individual Iranians psychologically and physically as they come to terms with the consequences of cultural loss: country, language, status, power, economic resources, uses of time, friends, relatives, and family structure.

Some Iranians manifest their cultural and social losses bodily through somatization and psychologically by withdrawal or anger, and clinicians often interpret these behaviors through their own cultural biases and professional traditions. This leads to misinterpreting patients' symptoms and perhaps misdiagnosing them.[1] The problem of interpretation and diagnosis of Iranian patients by Israeli clinicians was the basis of research conducted between 1978 and 1981, on which this article is based. Interviews were conducted with healthy and sick Iranians in Shirāz, Iran, and in Jerusalem, Israel, and with physicians, nurses, psychologists, and social workers in Israel. The Iranians interviewed in Shirāz were Muslim and Jewish, and those interviewed in Israel were Jews who immigrated from various cities and regions in Iran (Tehrān, Isfahān, Shirāz, Mashhad, Kāshān, Yazd, Bojnurd, and Kermān). The goal of the research at that time was to explain why Israeli clinicians had difficulties understanding, diagnosing, and treating their Iranian patients. The information gleaned from that study can be useful for American physicians treating Iranians of various religious backgrounds.[1] My intention here is to refine clinicians' perception of Iranian patients by explaining both dysphoric affects and beliefs about the body in Iranian culture, both of which reflect the themes of social and physical sensitivity.

Socially Sensitive Persons

Sensitivity is a highly valued trait in Iranian culture. It connotes personal, social, and aesthetic awareness, the last

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TRANSLITERATION OF PERSIAN VOWEL SOUNDS

"ā" in *nārāhat* pronounced as ä in father
"a" in *nārāhat* pronounced as ă in that
"e" in *esfand* pronounced as ĕ in sell
"i" in *nārāhati* pronounced as ē in feet
"o" in *ghoseh* pronounced as ō in cope
"u" in *khun* pronounced as ū in moon

being an appreciation for the poetry, music, and art that are so much a part of Persian culture. Social interaction in which people show respect and concern for the comfort of others involves the concept of sensitivity. In part, this has to do with *ta'ārof*—the ritual politeness code—and social hierarchy.[2] Respect and comfort are also elements that enter into social relationships, with the concept that the inner core of a person is sensitive.[1,3]

There are problems being sensitive, namely, that a sensitive person feels socially vulnerable and potentially powerless. Some people fear that exposing vulnerability will enable other forces—political, social, familial, economic, or spiritual—to impinge on their selfhood, enabling others to take advantage of them. Weakness or powerlessness also has a physical aspect in that sensitive people may also be weak regarding the physical environment and thus become sick. Because of these problems of sensitivity, it is important to speak kindly, softly, and courteously. Hospitality is given to others by offering tea to guests or to clients in one's office, thereby making them feel more comfortable. The failure to portray this sensitivity would not only reflect on a person's family and create an embarrassing social situation, but it could also engender *nārāhati*—being upset—in others.

Nārāhati (a noun; the adjective is *nārāhat*) is a general term used by Iranians to express undifferentiated, unpleasant emotional and physical feelings.[1] It is not entirely translatable. *Nārāhati* is used to denote a wide range of negative emotions, such as being depressed, inconvenienced, nervous, anxious, troubled, uneasy, worried, upset, disappointed, bothered, not tranquil, being in a bad mood, not feeling well, or restless. The adjective *nārāhat* is used in ordinary conversation to express and describe a variety of adverse feelings, both physical and emotional.

A sensitive person easily becomes *nārāhat,* and this could have social and physical repercussions, with the loss of status or role or the development of illness. With this in mind, the actions, reactions, and words of others are measured and evaluated. If it is possible that another will become *nārāhat* if certain information is revealed, this is done gently, perhaps over time, or maybe not at all. "Even if you want to cut off the head of a man," states a Persian proverb focusing on individual sensitivity and concomitant *nārāhati,* "do so with cotton and not with a sharp knife." So it is when disturbing news, such as someone's death, must be told to a relative abroad: This could take weeks, perhaps months, but decorum has it that the relative should not be alone when he or she hears of the death because the person not only could become *nārāhat* but could suffer from "fright" and thus become physically and perhaps emotionally sick.[3]

Because of everyday problems, sensitive people always encounter some type of *nārāhati.* This is especially the case with Iranian refugees who grieve for the country and culture they lost as they try to adjust to a new culture and social system. Untoward things happen that can cause *nārāhati.* What constitutes and causes *nārāhati* and how and to whom people express it often depend on a person's social and familial relationships, economic situation, and general physical health.

Expressing *Nārāhati*

Nārāhati is expressed in specific verbal, nonverbal, or aesthetic idioms—or not expressed at all. People's perceptions of their *nārāhati* influence whether they will manifest or hide it, express it verbally or nonverbally, or mask it consciously (or unconsciously). Revelation depends on the social context, where a person is, with whom, and what the *nārāhati* is. To verbally disclose a "private" *nārāhati,* something that a person feels is a personal problem, is a touchy matter: once again, it could indicate personal weakness or powerlessness, about which others are not trusted, or it could induce *nārāhati* in sensitive people, especially among close relatives and friends.

The *nārāhati* that is expressed verbally is often a "public" or common *nārāhati:* some situation or happening that others could identify with, possibly feel, sympathize with, react to, or help ameliorate, such as being *nārāhat* from not receiving a letter, from waiting in line for a bus, from hearing news on the radio, from an encounter with a friend, relative, or colleague, or from new shoes that give blisters. In this situation people use the term *nārāhat* to define the feeling and the situation that causes it. Frequently, however, people will talk about their troubles and the problems bothering them without mentioning the word *nārāhat* in reference to themselves, but they do use it in reference to others' behavior. For instance, while I was in Iran during the Islamic revolution, many Jews complained to me—a foreigner not affiliated with the community except by religious background—about Jews being *nārāhat* because of the political situation. In the company of friends and relatives inside the walled compounds of their houses, people sometimes spoke openly about being *nārāhat,* but more often they would talk about their problems and fears, never mentioning the word *nārāhat.* To non-Jews, of course, nothing was said because of mistrust that expressing their feelings would invite retaliation against the community.

More common than verbalizing *nārāhati* is expressing it nonverbally. The *nārāhati* expressed nonverbally is usually a private, personal problem, one that others cannot share or have not experienced in the same way as the person who feels distressed, such as specific family matters, economic troubles, or embarrassment and fear of failing school; or it may be a "public" societal situation of social or political events that persons are powerless to resolve, such as war. *Nārāhati* is idiomatically expressed nonverbally in three ways:

- Silence, quietness, and sulkiness, indicative of the sensitive person;
- Avoidance of food, signifying withdrawal from social interaction (as does the first) and possible physical danger;
- Sometimes, more among women than among men, crying, connoting emotionality, the exposure rather than concealment of feeling. "The wife gets upset immediately. She cries," explained an Iranian friend in Jerusalem. "The man goes to the crazy house. He holds it in more, and then he explodes."

In addition to the verbal and nonverbal expression of *nārāhati,* people may opt to mask their dysphoria by neither

talking about it nor displaying nonverbal signals. The rationale for camouflaging *nārāhati* is threefold:

- The concept that *nārāhati* connotes personal powerlessness that distrusted others could exploit;
- The belief that it sometimes signifies *qesmat*—fate—a situation in life with which one is stuck and can do nothing about (also related to feelings of powerlessness);
- The concern that exposing one's own *nārāhati* will make another person *nārāhat*. Masking *nārāhati* prevents intimates from becoming *nārāhat* and prevents nonintimates from knowing a person is weak or powerless.

Anger and Sadness

Two types of emotional expression—sometimes referred to as *nārāhati* but more often further differentiated into anger (*asabāniyat*, the adjective being *asabāni*) and sorrow or sadness (*ghamgini*)—are not masked. These two emotions are acted out in certain contexts and with certain people.

The adjective angry (*asabāni*) is derived from the Arabic word for nerve, *asab*. The term does not mean "nervous" but rather the condition of the nerves not functioning properly, which then creates anger. To be angry is to be out of control. In Iranian society, where self-control in social communication is prescribed, demonstrating anger could entail personal or familial embarrassment or shame, a possible breach in social relationships, or a damaged reputation. An *asabāni* person displays a lack of sensitivity to others, loudness and agitation, screams, does not respect others, and, in fact, makes those around him or her *nārāhat*.

Expressing anger toward others depends on a person's social relationships. Ideally, a person should not show anger by yelling or screaming at a person of higher status. For example, a child should not show anger to a parent, nor should a wife to her husband. In situations of reverse status, however, we can generalize that a father can express anger to his children, as can a husband to his wife or an employer to his employee. But care must be taken to whom and when anger is exhibited in public, even though persons who display anger are usually not held responsible for their actions. Outbursts are often blamed on "sick nerves." Although there may be causes for anger, like a pent-up *nārāhati*, if a person's nerves were not malfunctioning, the antisocial behavior of anger would not occur. Thus anger is considered to be a somatopsychic phenomenon, with possible social causes and definite social repercussions.

Sorrow or sadness, *ghamgini*, on the other hand, is a deeply felt *nārāhati*, one that can be "seen from the face." Sorrow, grief, sadness, worry—*gham* or *ghoseh*—are almost poetic feelings in Persian culture. Sadness expressed as conveying the tragedy of life is a valued emotion,[4] and many times the sadness of the human condition is expressed through the reciting of Persian poetry.

Grief, sorrow, and sadness are indicative of a loss—of a person, a livelihood, a country, or a desire—and can thus be more long lasting and fundamental concerning a person's inner essence than a temporary *nārāhati*. *Ghamgini* is a private emotion publicly expressed, suggestive of the sensitive person in a positive, social, aesthetic sense, connoting the external expression of what is felt internally. *Ghamgini*, as opposed to undifferentiated *nārāhati*, is valued as expressing the tragic in life, which is so much a part of the Iranian religious, historical, and aesthetic traditions. To declare grief or sorrow, verbally and nonverbally, does not connote personal weakness, as with a private *nārāhati:* the issues causing grief or sadness are the social problems deeply embedded in the Iranian social and cultural milieu and life in general—loss, death, and separation.[1] Refugees, especially, grieving for the loss of their country and culture, experience *ghamgini*.

Both anger and sorrow are types of *nārāhati* in which the external state reflects internal feeling; thus, they are differentiated emotions as opposed to the undifferentiated *nārāhati*. The undifferentiated *nārāhati* can be denied. Anger and sorrow cannot be. They are visible. Whereas anger is disvalued as disruptive and sorrow valued as profound, *nārāhati* is an emotion held private, ideally camouflaged in front of others, and rarely verbalized when deeply felt.

Somatization

When it is inappropriate or disapproved of to verbally or nonverbally express *nārāhati* or anger, some people somatize their problems.[1] The body becomes a metaphor for personal distress, enabling a person to become distanced from personal problems and to not assume responsibility for them, as the problems often are either not acknowledged or are not considered to be related to the bodily symptoms (Figure 1).

In Iranian culture, where people may be reticent to express private *nārāhati*, complaints about bodily discomfort—chest pains,[5] stomachaches and other digestive problems, and pains in the limbs—are commonplace.[1] The bodily complaints may be consciously used to manipulate others in distressing social situations. They may be actual pathologic disorders, or they may be real physical sensations through which persons somatize their affective states. According to the Iranian cultural conception of the human body and the individual manifestation of illness, the body is sensitive to various elements in the environment—climate, heat, moisture, and food. An imbalance in any one of these elements, such as an oversupply of heat or moisture, or the eating of too much of one category of food causes the body to react with some type of discomfort or *nārāhati*.

Food, Climate, and Illness in Iranian Tradition

The popular system of health care in Iranian culture is based on the Galenic-Islamic tradition of humoral medicine,[6] perhaps best elaborated by Ibn Sina (980–1037—known in the West as Avicenna), an Iranian who wrote in Arabic and a physician, philosopher, and poet who developed his system of medicine from Arabic, Greek, Latin, and Indian philosophers. According to Ibn Sina, two worlds existed, the perfect outer sphere of the stars, planets, and celestial beings and the sublunary world of generation and decay in which human beings, animals, plants, and minerals exist.[7] Their existence was dependent on compounds of the four elements—fire, air, water, and earth—and different proportions of the qualities of hot, cold, wet, and dry. The physiology of human beings, in addition, was determined by a balance between the four humors and their qualities: blood—hot and moist; red bile—hot and dry; phlegm—cold and moist; and black bile—cold and dry. Each person had a unique temperament derived from a distinctive balance of the four humors. Temperament, considered to be the physical constitution rather than the personality of a person, varied according to age (youths warmer, old people colder), sex (females colder, males warmer), race, and climate.

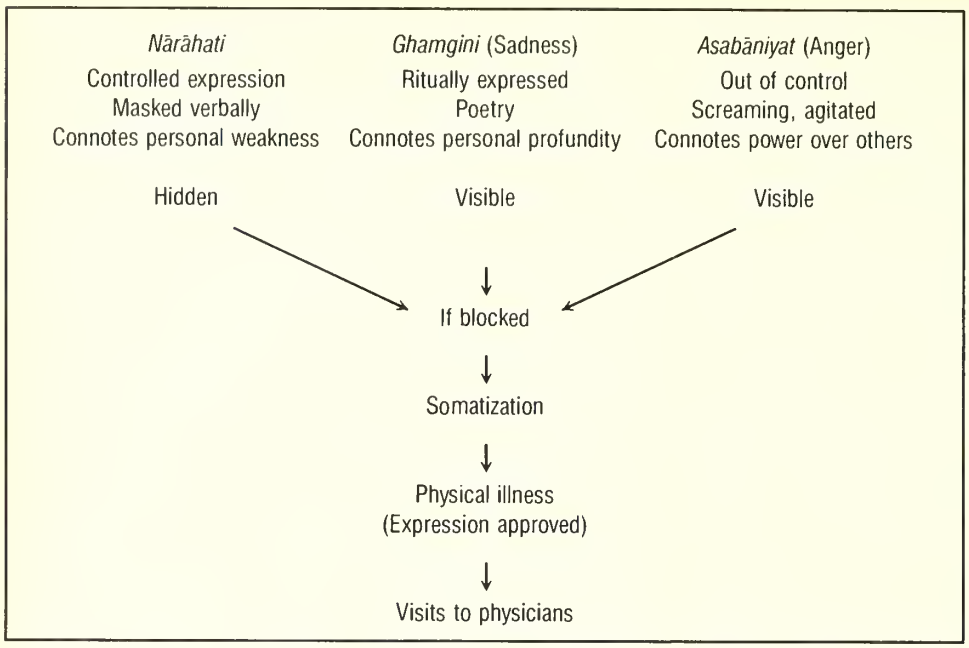

Figure 1.—The diagram shows the principal emotions that lead to somatization in Iranians.

Ibn Sina's precepts of medicine survive today in Iran and among Iranians abroad in the form of the hot-cold food system, conceptions of climatic influences on health, and notions of individual temperament. The qualities of hot, cold, moist, and dry in the maintenance of health are articulated not in terms of the humors but of food and climate as they affect individual temperament. As each person has a different temperament, what may be beneficial for one in terms of diet or climate may be harmful to others. Conceptions of the way the body reacts to certain aspects of the environment form part of the cognitive framework, which then influences physiologic reactions: those who believe that certain elements in the environment cause or cure sickness are more likely to get sick or well from these elements.

In Iranian culture all foodstuffs are categorized as hot or cold, with a number of foods classified as neutral, having neither a hot nor cold valence. The terms hot and cold refer to qualities, the essence or character of things. If too much of one quality of food is eaten, sickness could result. Health is maintained by diet as long as a person's individual equilibrium of hot and cold is not upset. Eating too many hot foods (or cold) can create a reaction that may be ameliorated by ingesting foods or herbal medicines of the opposite quality. Precaution is taken concerning the consumption of foods so as not to produce adverse reactions.

An imbalance in the hot-cold equilibrium of the body causes physical problems. Consuming too many cold foods in one day or at one meal, such as too many mulberries or several pomegranates, without eating an equivalent amount of hot foods (these amounts are judged according to the qualities of hotness or coldness contained within each particular food) can induce nausea and vomiting. To counteract this nausea, people drink tea, which has the quality of hot in addition to the hot temperature, with *nabat*, crystallized sugar akin to rock candy, which is considered to be very hot.

Eating too many hot foods at one time can cause headaches, rashes, pimples, sore throat, and sore mouth, although not all necessarily simultaneously. Which reaction a person gets from eating too many hot foods depends on that person's constitution. To counteract the effects of eating too many hot foods, people consume some cold food or drink, such as oranges, pomegranates, or *āblimu*, a sour lemonade. Certain physical problems resulting from the overconsumption of hot foods can be ameliorated by specific foods: headaches, citrus fruits and *āblimu;* pimples, *āblimu;* sore mouth, thickened pomegranate juice; sore throat, *āblimu*, sweet lemons (a fruit native to Iran), or hot milk.

Sickness is not caused solely by the overconsumption of one category of food, however. If someone does not feel well and if no dietary difference can be ascertained, then food is ruled out as the causal agent. Although foods might not have caused the symptoms, special foods and herbal remedies are used in Iranian folk medicine to treat the problems. Symptoms are not in themselves classified as hot or cold. A cough, for example, may or may not be due to the common cold; yet, some foods are bad for coughs and colds, such as pickles, which are cold, and sweets, which are hot; other cold foods, such as turnips, are considered beneficial for coughs. Stomachaches and nausea, which could be attributed to eating too many cold foods, may be caused by a malfunctioning of the gallbladder, which secretes too much bile into the stomach. This is considered the cause of nausea from motion sickness. Whatever the cause of the ailment, however, the same herbal teas or infusions are given: tea with *nabat* (rock candy) for a stomachache or nausea, *āblimu* for a headache or sore throat.

Herbal remedies are a major part of Iranian popular medicine. These include dried flowers, seeds, leaves, and berries that are steeped in hot water (or sometimes cold) and drunk for a variety of ills, ranging from digestive problems of nausea, stomachache, diarrhea, and constipation, to the more refined aspect of digestion, "cleaning the blood." In addition, there are herbal remedies for "cleaning the kidneys," gas, coughs, sore throat, bone aches, fevers, nerves, and fear. Some of the traditional medicines are used to treat a variety of sicknesses that may have different causes. Two of the most common of these all-inclusive medications are flat brown seeds called *khākshir* (London rocket-seeds, *Sisymbrium irio*) and dried purple flowers called *gol-i gāv zabān* (foxglove, *Digitalis purpurea*).[1] *Khākshir* is used for stomachaches, diarrhea, constipation, nausea, fever, and "dirty

blood." These tiny brown seeds are rinsed several times in water and then drunk with the water. They go through the digestive system undigested and are expelled whole, thus working as an abrasive, taking out with them the various poisons that are believed to cause the symptoms.

Gol-i gāv zabān is steeped in hot water and sometimes drunk with *nabāt* and is used for nerves, fear, pains of unknown origins, and blood. One man described his using *gol-i gāv zabān*:

For blood and fear. My wife's brother-in-law died of a heart attack. The whole family drank it because of fear and crying a lot. It is also good for blood. When the woman gets her period, she drinks *gol-i gāv zabān*. It gives strength.

One ailment concerning blood in Iranian culture is *kam khun* (blood deficiency). It develops from excessive bleeding, as in menstruation, from an accident or operation, or from an improper diet in which not enough blood is created. The main symptom of *kam khun* is physical weakness because there is insufficient blood to nourish the body. A well-nourished body is considered healthy and thus not prone to *kam khun*, although women of childbearing age are liable to develop it due to menstruation. Thinness, a sign of improper nutrition, is associated with *kam khun*. Because there is insufficient blood to nourish the nerves, a secondary result of *kam khun* is weak nerves, not in the sense of feeling lethargic but in the sense of *asabāni*, the nervousness that easily provokes a person to anger or excitability. The nerves malfunction and the person angers easily. Another result is headaches due to a lack of blood in the head.

Kam khun is treated with tonics, infusions, and foods, especially liver, lentils, and spinach, three foods high in iron. These foods in Western popular medicine are used to treat anemia. *Kam khun* may be analogous to anemia because both involve blood and weakness. The Iranian discourse of *kam khun*, however, is not concerned about the structure of the blood in the way anemia is. Rather, it concerns an entire range of ailments involving weakness, thinness, headaches, and nervous disorders. *Kam khun* is considered a physical ailment, and its manifestations are due to physical causes. In other words, weakness, lethargy, agitation, and irritability are considered somatic ailments, originating at times from a lack of blood. *Kam khun* exemplifies that a somatopsychic view of the workings of the body is more prevalent than a psychosomatic view. In fact, we may say that a somatopsychosomatic view of illness prevails.

Another ailment that many middle-aged and older Iranians suffer from is rheumatism. It is thought to be caused by living or working in damp, windy, and cool places. Thus, as derived from traditional Greco-Islamic medicine, the climate is the causal factor in this illness, moisture being the culprit. Moisture is associated with coolness and with winds. Winds (*bād*) can enter the body, create pains or cramps, and cause rheumatism or exacerbate it. Also, certain foods or food combinations are known to cause winds in the stomach and abdomen, such as eating yogurt and melon together.

Older men and women commonly complain about the pains in their limbs. When they were children, they say, and throughout their lives in Iran, they slept on a mattress on the floor, and the floor was cold and damp. Or they would bathe in the public bath or in a small pool in the family courtyard, "catch a wind," and get sick. Women are particularly prone to pains in their arms, and it is common to complain about the pains in a high-pitched voice, rub the afflicted area with the arm that feels normal, and attribute the pains to years of doing housework for their families.

What Should Clinicians Do?

As is often the case with refugees and immigrants who are uprooted from their culture of origin, Iranian refugees suffer from a variety of illnesses, some actual physical ailments (cancer or heart disease) and some somatized ailments, such as *kam khun*. Many Iranians may be experiencing depression, manifested emotionally as being *nārāhat*, *ghamgin* (sad), or *asabāni* (angry), and designated through somatization. Depression in Iranian refugees is a consequence of difficulties adjusting to the United States—family problems, financial predicaments, and communication dilemmas—all of which influence individual health, whether or not the patients are educated, rich or poor, Muslim, Christian, Jew, Bahai, or Zoroastrian. The problems of accommodating to a new society and the frequent *nārāhati*s resulting from it need to be taken into consideration by clinicians when treating Iranian patients.

Iranians in the United States may manifest depression, somatization, or real physiologic problems, and older, more traditional Iranians may do so in culturally distinctive ways, such as complaining about their pains in high-pitched voices, showing respect for physicians by speaking quietly, and bowing the head. Although many Iranians see no connection between personal problems and physical pain and often do not like to talk about their personal problems, acknowledging their social situation could be beneficial. For example, while taking a medical history, it may be helpful to ask the patient about difficulties adjusting to life in the United States:

How long have you been in the US? Do you miss Iran? Is your family here or in Iran? What kinds of things are difficult for you here in the US? How is your family—children, spouse, siblings, parents—adjusting to living here? I read something about *nārāhati*. Could you explain it to me? What kinds of things make you *nārāhat*?

To avoid making a patient *nārāhat* if bad news is to be conveyed (such as a diagnosis of cancer), care should be taken to provide this gently over a couple of visits. The kind of honesty regarding diagnoses that American clinicians are prone to use should be toned down and the family enlisted as support for the patient. The clinician could ask the patient about traditional remedies being used, such as *khākshir* or *gol-i gāv zabān*. If a drug is prescribed that is contraindicated for digitalis (*gol-i gāv zabān*), then the clinician should advise the patient not to take the herbal remedy while taking the prescribed drug. Otherwise, the clinician should encourage Iranians to take their own herbal remedies and to follow the hot-cold dietary regulations unless certain foods are to be avoided. It should be noted that in Iran there are few obese people, and this is probably related to following the traditional balanced diet.

Iranians in the United States represent a broad spectrum of the Iranian population. Because of the educational, financial, religious, social, and political differences among the Iranian refugees, clinicians must guard against stereotyping. Not all Iranians practice the hot-cold food distinctions or take herbal medicines; neither do people express dysphoria in the same ways. Whether or not their Iranian patients talk about emotional and physical sensitivity, how hot and cold foods and the climate influence the body, or the reluctance to express personal *nārāhati*, an empathic ear and learning to

listen cross-culturally will benefit clinicians trying to interpret the problems of their Iranian patients.

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* * *

Shadow and Echo and Jade

Perhaps only a single blossom
  from the whole bouquet will bloom.

Perhaps only a single, lonely cornstalk
  rises in the field.

Shadows cannot be held;
  echoes cannot be harnessed.

Poor work is an eyesore and obvious:
  it cannot be woven into music.

When the mind is caged and separate,
  the spirit wanders
  and nothing is controlled.

When the vein of jade is revealed in the rock,
  the whole mountain glistens.

Images must shine
  like pearls in water;

the thorn-bush, left unpruned,
  spreads in glorious disarray.

A common song sung to a great melody
is another way to find beauty.

LU CHI©
translation by Sam Hamill

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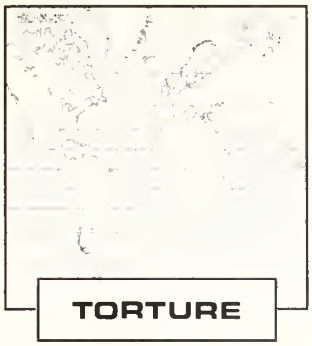
Cross-cultural Medicine
A Decade Later

- Almost 100 countries worldwide use torture as a means of social control and political oppression
- In 1988, more than 2.5 million refugees sought resettlement in Western Europe and North America because of war or torture



Working With Refugee Survivors of Torture

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Numerous factors must be taken into account to best provide for the health and well-being of refugee patients in developed countries. One issue that is rarely considered is the awful and not uncommon occurrence of political torture. Large numbers of refugees and other displaced persons are survivors of political torture, and health care professionals must be prepared for this possibility when treating refugee patients. The effects of torture are pervasive, and we provide some practical considerations for health professionals who care for survivors of torture. Specific challenges include problems relating to exile and resettlement, somatic symptoms and pain, and the "medicalization" of torture sequelae.

(Chester B, Holtan N: Working with refugee survivors of torture, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:301-304)

The real war is between our imagination and theirs. . . . Do not despair. None of them can see far enough, and so long as we do not let them violate our imagination, we will survive.[1(p99)]

During 1988, more than 18 million persons fled their homelands because of internal political strife. They left their communities and families because of starvation, war, and severe human rights abuses, including political arrest, arbitrary detention, torture, and the danger of extrajudicial "disappearance" or execution. Of this vast humanity, some 2.5 million people have sought refuge in the developed countries of North America and Western Europe.[2(pp4-6)]

Numerous factors must be taken into account to best provide for the health and well-being of refugees in developed countries, including the effects of torture in these patients.

Torture

The torture and ill treatment of prisoners is a profound and extreme form of trauma practiced by governments in almost 100 countries throughout the world.[3] Its purpose is to achieve complete social and political control by crushing and perverting relationships within a community of people. To do this, officials of a government or their agents strategically and deliberately destroy physical, social, emotional, and spiritual cohesiveness. Torture attempts to violate the soul, spirit, and imagination of a person by inflicting pain and suffering on the body and the mind. For the torture survivor, both internal and external reality have been irrevocably transformed:

> . . . [dealing with] the sometimes senseless questions for which there are no answers—and throughout, the anticipation and the fact of brute force, without limit, without end, the knowledge of being beyond the help of family or lawyer, of being totally at the mercy of those whose job is to have no mercy.[3(p18)]

Although other forms of trauma leave lingering and often chronic aftereffects, confrontation with the cold, calculated, and deliberate destruction of individuals, families, and communities is beyond the usual range of our imaginations. The surreal and bizarre images indelibly etched on the minds of survivors have been described as the "un-making of the world."[4] Torture is an inconceivable act, and, therefore, most health professionals have no conception of what torture victims have experienced.[5]

When caring for refugees or displaced persons, health professionals must keep in mind that they are dealing with many cultures, values, and worldviews. Although similar symptoms and sequelae of torture are registered all over the world,[6] the manner of treating these patients must take culture into account.[7,8] For example, two women patients, one from Laos and one from South Africa, showed severe symptoms of depression, anxiety, and nonspecific somatic complaints following torture. The Lao woman interpreted both her trauma and the attendant symptoms to interference by a sorcerer during her first pregnancy. She welcomed medical intervention as a more powerful and counteractive force against the spirits that continued to plague her life. The South African woman placed both her trauma and the process of rehabilitation in a political context and was not as open to the use of medication; in fact, she objected to the "medicalization" of her symptoms.

Health professionals must remember that the entire process of becoming a refugee is severely stressful and traumatic. This may have involved arrest, detention, and possible torture and imprisonment before flight; trauma during flight, including fear of discovery, starvation, disease, dangerous animals, and land mines; and the eventual limbo of refugee or detention centers. A clinic in Boston, Massachusetts, discovered through standard interviews that its Cambodian patients had all suffered 1 or more of 16 major traumatic events, 3 of which are defined as torture by United Nations criteria.[9]

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Recognizing the trauma history is particularly important in the health-related fields because of the mind-body interaction that is penultimate in all forms of extreme stress. Because patients and physicians alike tend to focus on the somatic results of trauma, and many of the patients' complaints are nonspecific, they may spend years in health care systems without finding relief from distressing symptoms.

Effects of Torture

Torture is defined as

> . . . the deliberate, systematic or wanton infliction of physical or mental suffering by one or more persons acting alone or on the orders of any authority, to force another person to yield information, to make a confession, or for any other reason.[10]

Survivors report that the worst experience is often not the torture itself but the anticipatory fear at the moment of arrest or between sessions of interrogation.[11]

Any aspect of humanity and self-identity is used against the victim in the cruelest and most painful way. In Tibet, for example, the invading Chinese forced celibate Buddhist priests and nuns to fornicate publicly.[12] Cambodian patients report receiving punishment for wearing eyeglasses or speaking the French language. Latin-American women describe sexual torture such as the insertion of objects, including insects and rodents, into their vaginas. Documentation also exists of the torture of children in front of their parents and torture of the fetus inside of the womb of pregnant women by forcing electric wires through the uterus.[13]

The consequences of such cruel treatment are extensive and affect every area of functioning. Pervasive fear, panic, shame, humiliation, nightmares, and physical pain accompany the survivor for many years. Spontaneous recovery from these symptoms appears to be poor.[14]

Survivors of torture tend to have symptoms in three areas: physical, psychological, and cognitive. In a 1990 report Rasmussen described the methods and the long-term effects of torture in a sample of 200 people examined during a seven-year period.[11] Commonly reported sequelae included skin lesions, lung infections, and tuberculosis due to poor conditions in prison; significant changes in the locomotor system, primarily due to beatings on the soles of the feet; severe headaches; gastrointestinal symptoms; bone fractures; dental problems; joint pain; and genital tract disorders in women. In addition, survivors complained of memory, concentration, and other cognitive disturbances. "Mental symptoms" including sleep disturbances, irritability, depression, and suicidal thoughts were registered in 68% of the survivors, and anxiety was common to all.[11] Psychiatric examinations of 41 survivors from three Latin-American countries elicited evidence of nightmares, insomnia, depression, anxiety, confusion, memory loss, and loss of concentration.[15] Other findings described regularly by health professionals who assess torture victims include lack of confidence and self-esteem, fear of intimacy, minimization denial, persistent shame and humiliation, despair, and loss of previously sustaining beliefs. Other symptoms, including nonspecific somatic complaints and emotional lability, are also common.[5,16-19]

Women and Children

Sexual abuse and rape figure prominently in the torture of women and girls. Reports from clinics and treatment centers in Boston, Toronto, Copenhagen, and Minneapolis indicate that a third to two thirds of women and girls seeking treatment for the sequelae of torture report incidents of sexual violation.[20] Amnesty International reports that women are vulnerable to rape and other sexual violation at all points in the process, from arrest and interrogation to refuge in detention camps that contain those seeking asylum.[2]

Children are direct and indirect victims of armed conflict. They are separated from their parents by the political imprisonment of their fathers or mothers. In countries such as the Philippines and South Africa, many young people have been detained and tortured. In South Africa, for example, more than 460 boys and 50 girls younger than 18 years were detained during 1977 and 1978.[21(pp95-98)]

Children and spouses of survivors also show long-lasting effects of trauma. Children suffer withdrawal, fear, depression, regressive behavior, sleeplessness, aggressive behavior, problems in school, and somatic complaints.[22] During the ongoing civil war in El Salvador, more than 100,000 children have been left homeless. A recent study of 349 children visiting a clinic in San Salvador revealed that a substantial number had gastrointestinal disorders, irritability, withdrawal, insomnia, and nightmares. Of these children, almost 60% had witnessed violence to family members, 4% had been direct victims of violence, and 88% were diagnosed as having anxiety.[23]

Challenges for Health Professionals

Substantial challenges exist in appropriately assessing and treating survivors of torture and their family members. Among these challenges are the extreme nature of the trauma, the fact that patients express their pain in the context of numerous cultural variations,[24] and the uncertain immigration and legal status of many displaced persons seen in medical settings in the United States. We describe other issues of concern as well.

Reticence to Talk About Their Experiences

Torture victims are initially reluctant to speak about their experiences, for several reasons:

- Survivors fear that they will not be believed, and the torturer reinforces this fear during interrogation;
- The torturer inflicts acts of such profound violation and humiliation that victims are ashamed to reveal the exact nature of their torments;
- Because of the phasic nature of traumatic memories, those tortured vacillate between intrusive and avoidance symptoms.[25] One patient was in therapy for six months before he was able to recall a particularly noxious torture session.

Because of this reticence on the part of survivors and family members, health professionals must consider the possiblity of torture when examining refugees or displaced persons, particularly if they show nonspecific somatic complaints or other symptoms of severe stress.

Profound Lack of Trust

Torture victims have experienced betrayal on many levels. They have been traumatized by agents of their own governments and, in many cases, by members of their own communities. On arrival in the United States, they face skepticism and disbelief and fear deportation. They also harbor serious and valid concerns about friends and family members left behind.

It is important to explain all medical procedures, including policies designed to protect patient confidentiality. Refugees who have been tortured often feel that their credibility is contained in their legal and medical records. File documentation should be explained in detail and treated with respect. A man from North Africa, for example, was proud of the thickness of his file and was devastated when a physician casually tossed it on his desk, said that he had no time to read it, and asked the man to repeat information already contained within the document.

It is also crucial for health professionals to follow through on all promises made, with clear and concise timeframes included. Alleviating symptoms with medication often can be an aid to building a level of trust and rapport.[26] The need to show respect to persons whose dignity has been so violated cannot be emphasized enough. Respect can be as simple as not keeping the person waiting for long periods of time.

Physical Sequelae of Torture

Because governments fear discovery, severely tortured prisoners are often confined until they are physically healed, or they are killed. In addition, more sophisticated techniques of torture, including drugs and psychological torture, are being used with greater frequency.[11] Health professionals must therefore be aware that chronic psychiatric indicators of distress, including depression and anxiety, may be signs of previous torture.

Sometimes physical signs of torture do exist, and health professionals must document them for the purposes of legal proceedings.[27,28(pp71-73)] Beatings, whippings, cigarette burns, searing with acid, and cuts with knives and bayonets leave scars consistent with their histories. Scars can also result from deep abrasions caused by shackles or bindings. Other physical evidence of torture may be found in healed fractures of long bones, damaged teeth, or healed punctured eardrums. A unique physical sequela of electrical torture is called in Spanish a *picaña,* a small white subcutaneous scar where electricity was applied to the skin. *Falanga,* a torture involving beating the soles of the feet, can cause skeletal deformity and scars. Other methods of medical documentation of torture now being investigated include electroencephalographic studies of sleep and dream cycles, skin biopsy to differentiate electrical from other sources of burn-related scars, and levels of serum creatine kinase and myoglobin in urine.[27] Survivors may need a physician's documentation of these objective physical sequelae for purposes of political asylum proceedings, civil suits for damages, support for intergovernmental investigatory bodies, or to support claims for reparation.[28(pp71-72)] Refugees and those seeking political asylum are defined as persons fleeing as a result of a well-founded fear of persecution.[29(p30)] Health professionals' support of this claim can make a tremendous difference in the ability of an undocumented alien to receive legal status in this country. Documenting mental health problems, including symptoms of post-traumatic stress disorder, is also gaining acceptance as valid evidence of a well-founded fear of persecution.[28(p72)]

Complicity of the Medical Profession

Health professionals should be aware of the possible complicity of medical professionals in the practice of torture. Such participation by physicians and psychologists has been documented in Chile, South Africa, the former Soviet Union, Turkey, and Uruguay. These acts of complicity range from falsifying death certificates to designing specific types of torture, monitoring, and actually applying torture.[30(pp64-65)-32] In addition, the policies and strategies of the government often make the country's health care systems unsafe for victims:

> . . . a deliberate policy of the security forces was to shoot people indiscriminately who attend demonstrations and then go to the hospital and wait for the injured to come in for treatment where they would arrest and detain them.[32(p127)]

Exile and Resettlement

During the past ten years, unprecedented numbers of non-English–speaking refugees have entered the United States. Various waves of refugees have arrived from Central America, Eastern Europe, the Middle and Far East, and Southeast Asia. Health professionals with patients who are refugees or displaced persons should read human rights reports such as the annual report published by Amnesty International. These advise where torture occurs during a given year and what methods of torture are documented. Torture is or has been rampant in countries as diverse as Afghanistan, Argentina, Cambodia, Chile, El Salvador, Ethiopia, Guatemala, Haiti, Iran, Nepal, Iraq, Romania, South Africa, Sri Lanka, Tibet, Turkey, and Uganda.

Torture has also become an exportable commodity. Amnesty International notes that torturers exchange information, methods, and equipment. Torture techniques are similar, with some cultural variations as to how these methods are applied.[33] This is true of all forms of torture but is most applicable to psychological torture where sex roles, spiritual values, and the reaction of the community are essential parts of individual identity. For example, in Bangladesh, the rape of a Muslim woman before the eyes of her husband or family is tantamount to a sentence of exile. For several tribes in South Africa, the prohibition against public gatherings significantly interfered with prescribed rituals around the grieving process.

Tortured refugees or those seeking political asylum tend to settle in areas of geographic access or in large cities. The states with the largest absolute numbers of refugees include California, Florida, Illinois, Massachusetts, New York, Texas, and Washington. The presence of large resettlement agencies in Minnesota and Wisconsin have resulted in concentrations of refugees, particularly from Southeast Asia, in these areas. People tend to join their communities in exile. A large number of Ethiopians, for example, have settled in Washington, DC, Los Angeles, and Minneapolis. There are more than 100,000 Guatemalans and 500,000 Salvadorans, most of whom are undocumented, residing in the border states of Arizona, California, and Texas.[29(pp64-65)]

Somatic Symptoms and Pain

Torture victims tend to describe physical rather than psychological or emotional symptoms as their chief problems. Pain, usually in the head, chest, or abdomen, is often their main concern. Pain symptoms can exist for months and years after torture. The pain may relate to a specific part of the body that had been traumatized during torture, including head trauma, electrical torture to the chest and heart, or forced water drinking and blows to the abdomen. Chronic low back pain was a symptom found in most torture victims evaluated in Denmark and the United States but does not

appear to correlate with specific trauma to the back, with hanging by the limbs, or with other abuse that might be expected to injure the back. Low back pain may be analogous to a tension headache.

For some patients, the pain abates after a careful medical examination, appropriate medical tests, and reassurance from a physician that there is no permanent damage from the torture—victims are often taunted during torture that their vital organs will be severely and permanently harmed. Some patients do not improve with reassurance, however, and require analgesics for pain. Gastritis exacerbated by psychological stress can make the use of aspirin or nonsteroidal anti-inflammatory agents inadvisable. Acetaminophen seems to work as well and is relatively safe.

Because of the poor camp and prison conditions they have endured, refugees and other torture victims are at high risk for certain infectious diseases, including tuberculosis, malaria, and intestinal parasites. They may have untreated or poorly treated orthopedic injuries, sensory deficits, or dental problems, and their immunizations may be scant or out of date. These patients need a complete physical examination while disrobed and gowned in order not to miss signs of torture or illness. Appropriate laboratory tests include blood counts; screening for hepatitis B, syphilis, and tuberculosis; and stool examinations for ova and parasites. Urinalysis, thyroid function tests, fasting lipid profiles, and stool tests for occult blood are also indicated for some patients.

Adequate investigation is essential to provide a correct differential diagnosis. For example, thyroid disease can masquerade as psychiatric symptoms or vague constitutional symptoms. Common symptoms of torture, including headaches, loss of memory, and concentration deficits, can be a result of depression or of neurologic damage resulting from head trauma. A man from Eastern Europe who had been given radiation while in detention and whose depression did not respond to medication was found to have severe hypothyroidism. In another case, an agitated and anxious man from West Africa who had been tortured was noted to have labile hypertension caused by hyperaldosteronism [confidential client-case files].

Conclusion

Health professionals must always consider the whole person, and this applies especially with refugees and other displaced persons who have been uprooted from their homes in a sudden and cataclysmic manner. Adding to the complexity of the situation are those patients who were not only displaced but tortured, as well.

Like torture survivors, the health professional assessing and treating these patients needs the courage to imagine. To facilitate the "re-making" of a survivor's world, the health care professional must recognize the multifaceted effects of torture and displacement on the individual, family, and community.

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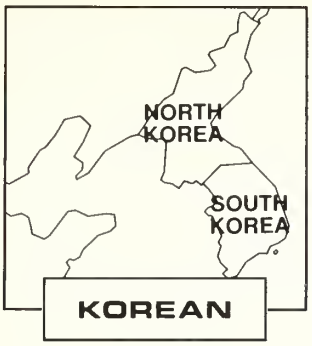
- 800,000 Koreans lived in the United States in 1990
- The presence in Korea of the US military spurred social change and encouraged migration to the United States
- Korean immigrants are relatively homogeneous in class, occupation, and religious affiliation



Cross-cultural Medicine
A Decade Later

This, That, and the Other
Managing Illness in a First-Generation Korean-American Family

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The use of Western medicine and of holistic traditional medicine and healing rituals is common in Korean-American families with a chronically ill member. I present a case as an example of the complexity of health management in first-generation Korean-American immigrants. Immigration and acculturation issues, Confucian-related sociocultural and psychological factors, and the psychiatric diagnosis of Western specialists all elicited family conflict leading to emotional and physiologic distress.

(Chin SY: This, that, and the other—Managing illness in a first-generation Korean-American family, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:305-309)

In Korea attitudes toward healing medications and the underlying belief systems perpetuate a pluralistic approach to health care. These multiple approaches to health and illness are not mutually exclusive but often are used together for different purposes.

Traditional herbal medicine or *hanyak*, embedded in Confucian notions, is used to create harmony in oneself in relation to a larger harmonious cosmology.[1] It is viewed as a way of healing both the soul and the body, of treating both the "ultimate causation" (usually spiritual) and "proximal causation" (usually material) of illness. It is the healing system preferred by older Koreans.[2] Another viable alternative is Western medicine, which alleviates symptoms, especially in emergencies like a broken leg and with problems that require technical expertise like surgical treatment. Western medicine and *hanyak* can be used alternately or concurrently.[3] Shamanistic healing rituals are another healing practice invoked to deal with particularly "difficult-to-define" illnesses or to ward off the possibility of misfortune when spirits are thought to be restless.[4-6(pp71-79)]

The case presented here was brought to my attention by a Western physician who was intrigued not only by the complexity of the case but also because translators were necessary for the large family meetings. I was not brought in to translate. As a bicultural, bilingual anthropologist, part of my fieldwork with the Korean-American community has entailed accompanying Korean elders to medical appointments. My function in such cases is to observe the group dynamics for the Western physicians and to provide additional information and possible insights into the situation. I present the case to illustrate these dynamics.

Report of a Case

The patient, a 29-year-old single man, lived with his lower-middle-class immigrant family that had been in the San Francisco Bay Area since 1975. The father was in building maintenance, worked hard, and had managed to buy a four-bedroom home in the suburbs.

A neuropsychiatrist reported that the patient was a sweet but psychotic epileptic man. He was referred from an epilepsy program because of episodes of irritability, psychotic ideation, and poor compliance with his pharmacologic regimen. The patient reportedly had little insight into his situation; his primary concern was shame over his lack of knowledge of the English language.

Medical History

The medical records indicated that the patient had enjoyed good health until June 1983, when at the age of 22 he underwent a surgical procedure for a urethral stricture. The operation itself was uncomplicated, but following the procedure, the patient was given a combination product containing sulfamethoxazole and trimethoprim and tonic-clonic seizure activity developed. Two months later, in August of 1983, he had an episode of status epilepticus resulting in a two-week admission to a hospital. The workup showed diffuse slowing on three separate electroencephalograms, but a computed tomographic head scan and a lumbar puncture showed no abnormalities. During this period, the patient was observed by staff to be "superstitious" and paranoid with a "delusion that he had been chosen by God."

The epilepsy persisted. Four years later, in February 1987, a right temporal lobectomy was done in an attempt to rectify the condition, but it was not successful.

According to a psychologist who had followed the case since 1983, there was no previous psychiatric history except for a neuropsychiatric evaluation in January 1987. The patient's verbal IQ was estimated at 77 and performance IQ at 70, after the intracarotid administration of amobarbital sodium to test for speech and memory. All tests were given in English, although it was noted that English was the patient's second language and that he had come to the United States from Korea at age 14.

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Psychosocial History

The patient was the only and therefore the first-born son in a family of four children. He had two older married sisters and one unmarried younger sister. He was born in Seoul, Korea, where he attended grade school and junior high school before moving to the United States. After leaving high school in the United States, he worked briefly at a gas station before the seizures forced him to give up work. There was no known history of childhood physical or sexual abuse. The patient's family shared a great concern over his well-being.

Course of Illness

September 1990. When I met the patient in September 1990 he had been living at home for the past seven years and had been unable to work. His younger sister, who also lived at home, reported that earlier in the year the patient believed that he could stop his seizures through mind control and ceased taking his medications. This led to a series of major motor seizures. The medical regimen at that time was 400 mg of phenytoin (Dilantin) per day and 45 mg of clorazepate dipotassium (Tranxene) per day. His medical records, however, indicated that he was intermittently noncompliant with this regimen.

In my first interview, the patient reported having had one to two seizures a day, each preceded by an aura of buzzing noise in both ears. When this sensation came on, he said he felt calm and went either into the backyard or into the living-room where he would lie down to have the seizure. If his mother was around, she provided him with a pillow. This was in contrast to prelobectomy episodes in which he had epigastric distress coupled with significant anxiety before the seizures.

The patient denied any episodes of violence directed at others. According to his medical records, however, he had struck a wall with his fist two years previously. His sisters also reported that after he had had several seizures, he became upset and violent and believed that people were "looking down on him." At these times, he also lost trust in his family.

I was introduced to the patient by the neuropsychiatrist at his office. I was to observe and comment on a follow-up evaluation of the patient's condition and to make sure that he understood the content of this appointment. On meeting the patient I was struck by his inability to articulate well in Korean or English, as well as the lack of logic to his statements in both languages. The language difficulties were, in part, attributed to the lobectomy. How much of the patient's thought disorder predated the lobectomy was unclear.

The patient was preoccupied by shame over his poor mastery of English, particularly compared with his three sisters. He said that he read all the time, trying to improve his English. Neither of his parents spoke much English. The patient said he felt sorry for his mother who was unable to leave home because of her inability to communicate in English.

He mentioned that his younger sister "thinks she [is] too good for me, and she's better than me. She's always showing off. I don't like my sister." He talked about the family's plans for finding a spouse for his sister and that his parents were arranging for her to be married. He then mentioned that all of his Korean friends had gotten married and that he wanted to get married and have a normal life.

On inquiring within the Korean community about the patient, I discovered that in 1979, just four years after migrating to the United States, his family had taken him to the Korean community center for counseling. In 1981 he had been referred to the Korean community center through a program for juvenile delinquents. His Korean-American social worker reported the following:

> Oh yeah, I remember him. He was really messed up. He was a very confused kid, rebelling against his Korean parents. You know, embarrassed about his background and doing really bad things like stealing cars or something. It's really hard for kids to come here at his age and adjust. His mother is such a nice lady. . . . She did everything she could. We tried to help, but it got to be too much for us to handle. I wondered what happened to him.

It is important to note that the patient had behavioral problems and contact with Korean counseling before his contact with Western medicine. Western medicine was the last resort for this family.

When I asked the social worker what the patient's mother did when she "did everything she could," the social worker recalled that the mother had gone first to fortune tellers to locate the source of her son's destructive and delinquent behavior. When that failed to abate his problems, she sought traditional herbal medicines that might soothe him. When those, too, failed to produce results (it is unclear whether this was because of noncompliance with the traditional herbal medical system), the mother went to the Korean community center for help. The patient's seizures began after these efforts at managing his behavior had not succeeded. Only then did the family decide to use the Western medical system.

October 1990. In October, the mother admitted her son to a psychiatric hospital because the patient had become so despondent and aggressive that she feared for her life. The father was in Korea trying to finalize arrangements for their youngest daughter's marriage. After the father returned but before the patient was released, a meeting was held with the patient's three physicians—a neurosurgeon, a neuropsychiatrist, and a psychiatrist—a neuropsychologist, two social workers, the parents, the three sisters, and me. My role was largely to observe, to provide culturally sensitive commentary to the physicians, and to intervene only when it seemed absolutely necessary.

The oldest daughter acted as the mediator and spokesperson for the family and the patient. Whenever the patient said anything, his sister would interpret what he said for the parents and for the Western health practitioners. I found this remarkable because the patient spoke in incomplete sentences that made no sense to me, but the sister was able to piece together his unfinished phrases and come out with a version of the story with which the patient seemed to concur. The sister and other family members seemed to be aware of his perceptions of the world and had learned to communicate with him. They had come to some understanding of the underlying logic of his thinking. It was unclear to me whether or not their interpretations were accurate or were a "cleaned up" version of the story for themselves or the physicians to minimize embarrassment and shame.

According to the oldest sister, before the violent episode that resulted in the patient's admission to hospital, the family's chief fear was that he would have an epileptic episode when he left the house. They wished desperately to avoid the commotion associated with an ambulance and transport to a local hospital. The patient, however, had recently been much more agitated about being kept at home. The sister who lived at home mentioned that on several occasions the patient had sneaked up outside the window of her room while she was

reading and repeatedly mouthed the words, "I'm going to get you." He had also yelled at his mother. Because the father was out of the country, the mother and daughters decided it would be safer for everyone if the patient were hospitalized.

During the meeting, the eldest daughter indicated that in Korea the patient had been a good student, athletic, and popular with his peers. When he first came to the United States, he tried hard to fit in. Both of the older sisters said that of all the children in the family, their brother seemed to adjust the fastest initially. At first his friends were all European-Americans and he seemed popular with the girls. Later, however, he fell in with a bad crowd of rebellious Korean-American teenagers. The family pinpoints this period as the beginning of the patient's behavioral difficulties, which have continued to be a problem ever since.

The attending physician raised some concerns about the patient's release from the hospital because he had locked himself in a bathroom and drunk a bottle of povidone-iodine and a bottle of hydrogen peroxide. When the patient was asked by Western physicians if he was trying to kill himself, he denied the incident had even happened. The attending psychiatrist said that a translator had been called in to talk with the patient and reported that the patient had wanted to kill himself.

The eldest sister said that the patient had told her that when he was in the hospital he did not believe he had legs; he thought his legs had been amputated (perhaps a way of saying he felt he had no standing in his family and was shamed by this?). She reported that the patient used the word "*chugesso*" and asked what was the point of living if he did not have legs? The phrases *chugesso* or *chugetta* are commonly used among Koreans. They do not carry the threat of suicide. During my initial interview with the patient, he had indeed repeatedly said to himself, *chugesso,* meaning "I could die [of mortification]," referring to his shame about his condition. The sister suggested that the patient spoke in an unusual manner and did not make much sense to others and that a poor interpretation or translation of his speech patterns may have led to the physicians' misunderstanding the seriousness of the situation. To the physicians, *chugesso* ["I could die"] could have been seen as a death threat or a sign of suicidal intent rather than as an expression of shame or embarrassment. The sister went on to state calmly that the patient did have violent outbursts and that the family was used to dealing with them. Furthermore, although he had drunk the cleaning chemicals, it did not mean that he had tried to kill himself. The family believed that he simply did not know what he was doing at the time. (According to one psychologist, the patient seems to have had violent outbursts during his seizures about once every six months.) The sister also noted that in the past—as in this instance—many of the patient's statements had been interpreted out of context. She asked me to verify her interpretation of the meaning of the term "*chugesso*," which I did. It was not clear, however, if the family wanted to downplay the incident because it caused them to lose face or if that was, indeed, how they perceived the situation.

During the discussion of the patient's alleged suicide threat by the Western practitioners and the patient's sister, the rest of the family spoke among themselves about the father's recent visit to Korea and his unsatisfactory visits with various *jomjeangis* (fortune tellers) about the patient's problems. The father had finally found a *mansin* or shaman who seemed to make sense. Consultation with the shaman revealed that the grave site of the father's parents was inauspicious and because of that the patient might be "possessed." Great concern was expressed by the family about locating the right geomancer to find the appropriate space for a reburial and about the associated costs.

In Korean society, when divination is used to diagnose sources of mental or chronic illness, it is not uncommon to blame supernatural beings, mainly dead ancestors or other gods and demons.[7,8] "Possession" is not the only or even the most common way that ancestors, spirits, and ghosts are believed to influence a living person, but it is one possible explanation for the types of seizures and violent fits that the patient was experiencing.[5,9] The father, who is the eldest son in his family, thought that this might be a valid issue because he had neglected his parents' grave sites for some time.

The final decision of the family meeting was that the patient would go home and the mother would control his medications. In conversations in Korean among the family members, it was revealed that the father had brought back four types of traditional herbal medications for his son to take in addition to the medications prescribed by the physician because the Western medicine alone was not "curing" his son. The family clearly thought that the use of both Western and traditional Korean medicine was not in any way harmful. At this point I intervened and asked the sister to explain to the physicians what herbs they were going to give the patient. She insisted that they were "just herbs" and not harmful. Two of the physicians seemed aware of the family's occasional use of traditional herbal medicine but not of the full extent of it. When the physicians realized that the family had been medicating the patient on their own, they asked the family to bring in the traditional herbal medicine for analysis so that possible drug interactions could be evaluated. Neither the family nor the practitioners followed through on this request.

The family seemed to want to do everything possible to help the patient, including making plans to move the grave site of the father's parents. After the meeting, the family confided to me that all of the members were emotionally exhausted from dealing with the patient's chronic problems. The parents said that they were physically exhausted as well. The mother, once an active member of a Korean church, had stopped socializing in the community. The entire family was feeling ostracized by the rest of the Korean community because of the patient, who first was delinquent and then an epileptic psychotic. The two older sisters also mentioned that they continually had to take time off work to deal with the ongoing crises and that they both had conflicts with their husbands because of the attention their brother required.

November 1990. In November, a second violent episode occurred in the household. The patient came into the kitchen one evening, grabbed a knife, cut the phone cord, and entreated his parents to commit a joint suicide. When they refused, he threatened to kill both of them first and then himself. Both parents got down on their knees and pleaded with him for their lives. When the patient started to cry the mother managed to run out of the kitchen and call the police. The patient was admitted to the hospital involuntarily for 72 hours of psychiatric observation.

After this episode, the parents refused to take the patient home, so the hospital stay was extended two weeks until placement could be arranged. Another family meeting was held with the three physicians, the neuropsychologist, the

three social workers, the entire family, a visiting aunt, myself, and a health care worker. Family members finally admitted being unsure of what the patient meant when he talked and confessed that they were now afraid of his violent outbursts. Responsibility for the patient was shifted to local health care officials. Although placement in a residential care unit was difficult because the family lived in a different county from where he was hospitalized, this was eventually accomplished.

April 1992. A year and a half after discharge from the hospital to a residential care unit, the patient got upset when an attendant gave him his medication because he said he was being given "too many pills." He shouted at the attendant, pushed her down to the floor, and lifted a heavy paper punch as if to attack her. As a consequence, the patient was moved to the psychiatric ward of a hospital.

At the time of this writing, three residential options were being considered: return the patient to the residental care unit, admit him to Napa (California) State Hospital for life, or put him in a locked psychiatric unit until an alternative living arrangement could be found. The family had arranged to move the grave site of the father's parents in the summer of 1992. Geomancers were consulted in planning the move of the graves. The youngest daughter had returned to Korea to try and find a man who would marry her despite the shame and stigma of having a chronically mentally ill brother. The mother was near collapse and had withdrawn from the wider Korean community, which was increasingly uneasy about the shame the patient was bringing to them all. The father was disengaged. The eldest sister reported that he was having memory problems, although he claimed that he was not but was just "sick to death" of dealing with his son.

Discussion

The problems of this family are far from resolved. Given the severity of the patient's condition, there seem to be few options for this family. Consultation with the *mansin* (shaman) in Korea brought some relief to the older generation, who were still waiting to see what would happen when the ancestral grave site was resituated with the help of a geomancer.[10] Only after discovering the inauspiciousness of the grave sites was the family able to relinquish some of the responsibility for the patient's care and allow Western health care professionals to manage the case. This does not mean that alternative modes of healing have been abandoned, only that while the family waited for the relocation of the grave site, they would leave his care to local authorities.

This particular case is complex because of the various levels on which the patient's illness was perceived, presented, and treated. The family elected to use all of the alternatives available to them to help their son, but there was a difference between the attitudes of the parents and those of the three sisters. Although the sisters complied with their parents' wishes and did not describe the other forms of treatment they were using for the Western health-care professionals until I insisted, the women repeatedly entreated their parents to "listen to the doctors" and to try to use just one form of medication. After I asked the eldest sister to tell the physicians about the alternative healing practices that they were using, she asked one of the physicians why it might be a problem to use both traditional herbal and Western medicine concurrently since traditional medicine was "just herbs." The sisters were unwilling to translate the conversation between their parents and aunt about the *mansin*'s (shaman's) assessment of the patient's disorder. They appeared uncomfortable and mentioned the inauspicious grave sites to the Western physicians only because the father insisted.

Other contributing factors to management of a first-generation Korean-American patient are the Confucian-related sociocultural and psychological factors that may elicit conflict and lead to emotional and physiologic disorders in a family member.[11,12] The patient was the first and only son, and expectations for a son far exceed those for daughters in both work and family responsibilities. There is pressure for the eldest son to make something of himself, to provide an heir to the family line, and eventually to take care of his parents. The patient's entry into the United States at age 14 was not easy, and his delinquency in his late teens and early 20s attests to a period of rebellion against this new society and against his parents who represented traditional Korea. During my initial interview with the patient, he expressed great sorrow that all of his Korean friends (with whom he used to steal cars) had left him about three years before when they had gotten married and started their own families and households. This was the final severing of any sense of community that he had found in the United States. It also heightened his differences from his peers and his inability to perform adequately the roles expected of him.

Birth sequence reflects ordering of life events.[11] A failure to live up to these standards is a source of conflict in both the patient and his family. When the two older sisters married and had children, the patient was not particularly upset because it is expected that siblings marry in birth order. He seemed to trust the eldest sister and was indifferent to the second-born sister. The patient felt tremendous rage, however, toward the youngest sister who lived at home with him. Being the elder brother, he thought that he should have been better than this sibling. The sister, however, was managing much better than he was and was still seeking a husband in Korea at the time of this writing.

Finally, the effects of migration on families and on the mental health of their members cannot be ignored. The necessary restructuring of values and ways of life are accompanied by a tremendous acculturation stress that may affect families differently.[13-15] Adaptation to the United States was not easy for this family. The family was well aware that US society was somewhat hostile toward non-European Americans. Talking among themselves in the family sessions, the parents expressed sentiments about the difficulties of living here. The patient's three sisters concurred with these sentiments. The two older sisters married first-generation Korean men, and the younger sister intended to marry a man in Korea because she wished to live there. The entire family agreed that they did not want to be noticed publicly. The fact that the son had seizures that brought attention to them created great distress for the family. There was tremendous shame associated with the patient's chronic mental health problems. The family has tried to keep the problems in the family.

Several issues are raised by this particular case. First, with the influx of non-Western immigrants to the United States, there is a need for medical professionals here to recognize and understand non-Western medical systems and attitudes toward health and illness. Many healing resources—traditional and Western—are available to first-generation Korean-American families. In a psychiatric context that encourages the family to reveal details of a patient's

disorder because it will help the family deal with the problems, the family in this case tried to cover up the extent of their family member's illness to save face. Furthermore, this family placed its hopes on traditional modes of healing. Traditional and Western medical practitioners need to work together in designing treatments for patients and families who are not of European-American descent.

Second, the issue of overmedication is real. The patient reported here might have been overmedicated inadvertently because of the multiple treatments his family sought for him. Traditional Southeast Asian and Asian medicines might be "just herbs," but herbs can have great potency and cause drug interactions when used in combination with Western medications.[16,17] It behooves health professionals to follow up more closely when traditional medicines are being used.

In negotiating the Western medical system in the United States, first-generation immigrants need a cultural interpreter, not just a translator.* Often a translator merely explains words from one language to another without attending to the underlying belief system of the culture. As in this case, many misunderstandings can ensue.

Finally, this case study brings up the compounding factors of migration and acculturation stress; both have bearing upon the initial symptoms of mental and physiologic disorders.[14] There has been a shift toward Western medicine among Korean Americans, particularly among young cohorts of first-generation Korean Americans who have been educated and spent most of their lives in the United States. The biomedical approach is not the sole system of treatment but is used in combination with *hanyak* and other types of healing rituals, which vary greatly with age, education, and socioeconomic status. According to Pang, health and illness practices in first-generation Korean Americans can be most accurately described as pluralistic in nature.[2] This pluralistic nature can add to intergenerational conflict and family disintegration when family members with different views toward health and illness are forced to deal with problems such as chronic mental illness. Given this multifocal approach to health and illness and the different views about health practices that can exist within one family, it is critical for Western health professionals to work with or at least understand beliefs about health practices of other cultures so that healing can occur.

*See also L. Haffner, "Translation Is Not Enough—Interpreting in a Medical Setting," on pages 255-259 of this issue.

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- About 150,000 Laotians live in the United States
- When the US withdrew from the Southeast Asian conflicts in 1975, some 13,000 Mien fled the rural highlands of Laos for Thailand
- In 1980, asylum in the US was granted the Mien in camps in Thailand

Cross-cultural Medicine
A Decade Later

Use of Traditional and Modern Health Services by Laotian Refugees

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Although refugee health care emerged as a special interest in the United States following the influx of almost a million Southeast Asians since 1975, few studies have been done of the influence of refugee traditions on the use of Western medical services. The illness patterns, medical beliefs, and health care behavior of a Southeast Asian refugee group, the Mien from Laos are described in this study. A cohort of 119 Mien refugees living in Richmond, California, was observed for a 6-month period. In-home interviews were undertaken about all episodes of ill health, including treatment and health care decisions. This study shows that the Mien integrate traditional healing beliefs and practices with the use of American health services. Such findings are important because the increasing cultural diversity in the United States, particularly in Western states, necessitates that health care professionals understand the importance of cultural factors for access to and the use of health care by all patients including refugees and other immigrant groups.

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Refugee health care has emerged in the United States as an area of special interest following the influx of almost a million Southeast Asians since 1975. Because the largest number of Southeast Asian refugees resettled in the US West, health care professionals, particularly in California, Washington, and Oregon, have confronted numerous challenges in providing medical care to this population. Earlier articles focused on new refugees and the need for "health screening" for infectious and other tropical diseases.[1,2] Reports providing brief, general descriptions of Southeast Asian cultures, including traditional practices, beliefs, and attitudes towards health and medical care, appeared in medical journals with the early arrival of refugees.[3-5] For example, a photo of a Mien family in full traditional dress was on the cover of THE WESTERN JOURNAL OF MEDICINE's initial special issue on cross-cultural medicine in December 1983.[4] Few articles have been published, however, about the influence of refugee traditions on the use of Western medical services in US communities.

Research Methods

Most physicians and other health care professionals meet refugees only in clinical settings and thus do not have access to information about factors influencing Southeast Asian patients' definition of illness and treatment-seeking behavior. The present study was designed to help fill this gap in current medical knowledge about the refugee community by describing the illness patterns, medical beliefs, and health care behavior of one Southeast Asian refugee group, the Mien from Laos. A research team of two physicians (S.C.G. and G.C.), a Laotian university student (K.S.), and an anthropologist (J.J.) collaborated on a community-based study in 1988 to 1989, observing a cohort (randomly selected from telephone book listings) of 17 Mien refugee families with 119 household members. The first six-month phase of this two-part study consisted of ethnographic in-home interviews of Mien families, healers, and religious leaders and interviews of health care professionals at voluntary agencies and medical facilities providing services to Mien. Traditional and Christian Mien religious ceremonies were observed in Mien homes and in the Mien church. Phase two consisted of biweekly surveys of all episodes of ill health and treatment during the subsequent six-month period. One member of each household served as the principal informant on health for all persons in the household, aided by other family members who were usually present during the in-home interviews. The Mien researcher conducted interviews in the refugees' own language. The findings of this study provide insight into how refugees integrate traditional healing beliefs and practices with the use of American health services.

The Mien

This study of Mien in Richmond, a city in the San Francisco Bay Area of California, is one of the few community-

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based cohort studies of refugee use of health services to consider traditional health practices. Richmond's Mien population is estimated to number between 1,200 and 1,500. Although there are many Southeast Asian groups in the San Francisco Bay Area, the Mien were selected for study for several reasons:

- Mien are identifiable at the community level because of naming practices. The Mien naming convention in the United States places the prefix "Sae" on all clan names. Only six clan names—which serve as the second or family name in the United States—are used in the research area: Saepharn, Saeteurn, Saelee, Saechao, Saefong, Saeliaw, and their spelling variants;
- The Mien refugees are similar in educational and economic status because they came from a homogeneous highland rural culture in Laos. They were one of the most geographically isolated groups before emigration and, therefore, had greater difficulties adjusting to this country than did other Southeast Asian refugee groups who are from lowland and urban areas;
- The Mien were accessible to the research team because one team member is a Mien refugee who lived in Richmond with his family. He was the first member of the Mien community to attend the University of California at Berkeley where he was a third-year undergraduate student at the time of this study (1988 to 1989).

Data about Mien use of health services are not easily compared with those of other Americans because of economic, family structure, and demographic factors. Strand and Jones's cross-sectional study found that Hmong refugees, another highland Lao group with many cultural similarities to the Mien, were infrequent users of Western medical services compared with other Southeast Asian refugees.[6] Unfortunately, the authors did not address the use of indigenous healing practices. Brainard and Zaharlick sampled ethnic lowland Lao from a voluntary agency roster in Ohio and found little traditional healing activity among this population.[7] Buchwald and co-workers, however, found the frequent practice of traditional healing among Southeast Asians in Washington State.[8]

Background

The Mien, also called "Iu Mien" or "Yao," are a highland people who inhabit the hills of Vietnam, Thailand, Laos, Burma, and China.[9] The Mien migrated to Southeast Asia from southern China over several hundred years and still retain many features of Chinese tradition. Mien religion includes aspects of animism, ancestor worship, and Chinese Taoism. A Chinese dialect is used for the Mien's religious language, and written records are recorded in Chinese characters. Other hill people in Laos, such as the Hmong, do not keep written records.

Life in the highlands of Laos consisted of slash-and-burn agriculture, frequent religious rituals, and war that extended for a period before World War II through 1975.[10] Western-style medical services available in Laos were poorly developed, especially in the hills, and Mien and other hill tribes relied primarily on traditional healing before emigrating from Laos.[11]

The Mien who lived in Laos sided with the United States and other allies against Communist forces in the region from 1959 to 1975 during the war in Southeast Asia. When the United States withdrew from Southeast Asia, approximately 13,000 Mien living in Laos fled to Thailand.[12] In 1980 the US made asylum widely available to the Mien who were in refugee camps in Thailand.[13] Although the Mien initially were settled throughout the United States, their sense of family, village structure, and religion, in addition to differences in public assistance benefits among the US states,[12] contributed to a second migration and resettlement to the West. About 15,000 Mien are currently living in the US, although accurate demographic information is impossible to obtain because the Mien are counted as Lao, a category that also encompasses the culturally distinct Hmong, other hill tribes, and the lowland or urban Lao.

The Mien who settled in Richmond reside in poor urban neighborhoods in this city of approximately 92,000 people. Study participants generally live in poorly maintained rental apartments and small houses on streets with decaying and abandoned buildings. Households usually comprise an extended family consisting of two and three generations and, on average, seven people. Most Mien families are poor and receive welfare benefits. Several families supplement this income with day work as manual laborers, gardeners, house cleaners, babysitters, and so forth. For most, a lack of formal education and fluency in English are barriers to other employment. Among the 17 families participating in the study, only 2 were comfortable speaking English, and even these families resorted to Mien for the discussion of any complex issues. Children attend the local public schools where they learn English, but most adults still use the Mien language, especially in the home.

Findings

The combination of home visits, interview schedules, and observation of relevant Mien traditional ceremonies provides a comprehensive picture of health problems and treatment practices of the 17 households with 119 family members. Study participants ranged in age from 2 months to 74 years, with a skewed age distribution, 69% being younger than 18 years. Their average age was 20.3 years, and the median age was 10 years. Just over half (52%) of the sample was female.

Religion is a factor influencing Mien health beliefs and practices. Of the participants in the study, 72% practiced Mien religion and 28% were Christian (Baptist). Some Mien converted to Christianity in the Thai refugee camps because of a rumor that only Christians could immigrate to the US. Others converted in Thailand or the United States because family members no longer knew the traditions or the loss of the family's written religious records containing the spirit names of ancestors prevented them from conducting traditional ceremonies. Some Mien converted because they thought it would help cure illnesses.

Illness Symptoms

During the study, 66 people reported 174 episodes of illness. Some illnesses had constellations of several symptoms and, therefore, the occurrence of 232 symptoms for the 174 illnesses was reported. As expected, the incidence of symptom reports varied by age group, the highest incidence occurring among the youngest and oldest age categories, shown in Table 1.[14] Respiratory symptoms were the most common, accounting for 45% of the total symptoms and 51% of the symptoms in the youngest age group.

Symptom categorization was open-ended to include everything participants classified as a symptom of illness. For example, "soul fright" was reported once for an infant. Soul fright is a cause of "soul loss," which is a symptom complex of sleeplessness, distractability, and listlessness believed to indicate that the soul has been frightened from the body. Mien experience more symptoms of headaches and musculoskeletal complaints than might be expected from the general population. These two symptom categories are frequently attributed to a somatization of depression or post-

TABLE 1.—*Primory Symptom Type in a Mien Community (n=66) by Age Group*

Symptom Type*	Age Group, yr < 5	5-18	19-64	> 64	Total
Abdominal pain	3	0	6	0	9
Cardiovascular	0	0	1	0	1
Ears, nose, and throat	1	2	1	0	4
Gastrointestinal	5	1	8	1	15
Genitourinary	2	0	3	0	5
Headache	2	2	5	1	10
Miscellaneous	7	1	5	1	14
Musculoskeletal	1	0	13	3	17
Respiratory	48	8	14	8	78
Skin	9	0	5	6	20
"Soul fright"	1	0	0	0	1
Total	79	14	61	20	174
No. of persons in age group	36	33	44	6	119
Symptoms/age group, %	45	8	35	11	

*Categories adapted from National Center for Health Services Research.[14]

traumatic stress disorder and are responsible for many refugee visits to health professionals.[15] The study only collected information on reported symptoms and did not attempt to assess physical or mental health. Mien find it hard to understand mental illness; in fact, the Mien language does not have a word for mental illness. When consulting a physician, Mien expect to receive physical treatment—that is, medicine or injections—and therefore generally do not perceive psychotherapy as treatment.

Treatment Practices

Western Medical Treatment

General medical treatment was available from several sources. The two public clinics in Richmond include a county-supported clinic and a neighborhood health center. Public medical specialty clinics and inpatient care are available at the county hospital 20 miles away—a long trip on public transportation. Private sources for medical care include a local hospital and any community physician who accepts Medi-Cal (California's Medicaid program). Many private physicians in California do not accept Medi-Cal because of the low reimbursement rates. Most study participants were covered by medical insurance, 86% by Medi-Cal and 10% by private insurance; 4% were medically uninsured.

Most of the private Western-trained physicians used by the Mien were described by them as ethnic Chinese. Mien said they consulted private Chinese physicians because, unlike public clinics, they would provide antibiotic injections on request. Injections are a popular form of treatment among Southeast Asians and other populations in developing countries. In addition, many Mien read and write some Chinese, which facilitates communication during consultation with the Chinese physicians and provides a more culturally familiar context. Some Mien traveled as far as 50 miles to consult the Chinese physicians in Sacramento and other cities.

Although public health care services in Richmond are available, patients reported problems with long waiting times and difficult and costly travel to reach services. In addition to other cultural differences, language posed a major problem. Richmond's two public clinics both have Mien language interpreters but only on a limited, scheduled basis. Mien patients who come to the clinics for urgent or walk-in care may not find interpreters available. If patients were not able to attend the clinic when interpreters were available, they often relied on a school-age child who spoke English. Health care professionals interviewed at the public clinics reported that language difficulties and misunderstandings about treatment were barriers to the optimal use of health services for the Mien and other Southeast Asian patients.[16]

Treatment was obtained from physicians for 77 of the 174 episodes of illness, from physicians in public clinics and neighborhood health centers for 60% of these illnesses, in a physician's private office for 27%, and 13% were treated in a hospital emergency department. Only seven admissions to hospital occurred during the study. Treatment was not sought by 9% of the participants reporting illnesses.

Medications were a frequently used treatment, 65% of the participants saying they used some medication, and many reported using more than one drug to treat the same illness. Medications were obtained from a variety of sources, including pharmacies, physicians' offices, grocery stores, and medicines already in the home. Mien often sought medical advice from Asian-American shopkeepers and purchased over-the-counter medication, several illegally imported from Thailand, Hong Kong, and Canada. A visit to an Asian shop in the Richmond area revealed several products either not approved for use in the United States or that should be dispensed at a pharmacy by prescription only. Health professionals in both public and private medical facilities treating the Mien were unaware that patients might be taking unapproved and controlled medications that could have notable side effects.

Traditional Treatments

Several types of traditional care are used by the Mien, including self-care and home remedies, herbal medicines, and healing ceremonies. These non-Western treatments are selected based on the perceived causation of the illness: physical, humoral imbalance, or spiritual. Religious preference for either Mien religion or Christianity also influences the use of traditional treatments. Most Mien healing practices involve appeals to traditional spirits and ancestors, the exception being the use of home remedies and herbal medicines and of interventions related to humoral theory. Examples of these healing practices and descriptions of the more important healing ceremonies provide insight into the integration of traditional and modern medical practices.

Traditional therapies for illnesses attributed to a physical cause. Traditional therapies for symptoms that are thought to have physical rather than spiritual causation include home remedies, herbal medicines, and humoral-related treatments. Religion is not a factor here. Many home remedies are related to diet—for example, drinking a special tea or abstaining from certain foods.

Herbal medicines are popular. In Laos they were prescribed mostly by older women with special knowledge about their use. In the US the use of herbal medicines is limited by the availability of herbs, although some people in Richmond keep herb gardens. Some traditional Mien herbs are obtained from friends or relatives in Thailand. Herbs obtained from vendors in San Francisco's Chinatown, although different from Mien herbs, can be adapted for use. Herbal medicines were used by the study population to treat 12% of reported illnesses, often for respiratory symptoms. They obtained the medicine from another Mien in 17 of 21 of the cases (81%), which suggests that the dispensing of herbal substances by an expert continues in this country. Herbal ingredients were grown by three of the patients (21%), and only one (5%) obtained herbal medicines in Chinatown.

Traditional treatment of sar *conditions.* Traditional therapies are used for *sar* conditions, which are attributed not to ancestors or other spirits but to humoral imbalance. Physical interventions used for *sar* are common throughout Southeast Asia. There are several forms of *sar* treatment. One is "cupping": A cup filled with burning paper is placed over the affected area, and the fire burns off the oxygen, leaving a circular red mark on removal. In a second form, pinching or "catch *sar,*" pinches are made on the skin over the affected area, chest, neck, or back. In a third method, fine scratches are used for some specific illnesses. Mien believe these treatments will remove "hot blood" from an area and cure certain musculoskeletal and abdominal complaints. Most Richmond Mien do not use *sar* treatments—only five people in the study group used it to treat 9% of the reported illnesses. Wick burning was used in six cases, cupping in five, and skin pinching was used twice. *Sar* can be disfiguring and may be misinterpreted as physical abuse.[17] Many Mien said they would not use this treatment on their children, even if it was thought to be beneficial. They feared accusations of child abuse by medical and school personnel who observed the bruises and other marks from *sar* treatments. Among the five patients who had *sar* treatment, however, two were children ages 5 and 10. The 10-year-old child lived in the household of a frequent *sar* user.

Traditional therapies for illnesses involving spiritual causes. Traditional religious healing ceremonies are an important dimension of Mien culture. Several traditional ceremonies are used for healing and other purposes, such as for protection from evil spirits, disasters, and bad dreams. Although Chinese and Mien New Year ceremonies are nonhealing ceremonies, they are healing related because they confer health benefits on all family members.

Sip mmien. The *sip mmien* is both a healing and protective ceremony. In the Mien language the word "mien" means "people" and the word "mmien" means "ancestor spirits." *Sip mmien* is a general name for more than 14 different ceremonies used by the Mien for healing.

The types of ceremonies vary widely, and each can be used for a variety of purposes. *Sip mmien* ceremonies were used in 19% (33/174) of all reported illnesses. Mien practicing the traditional religion performed *sip mmien* for healing illness in only 25% of cases. Ceremonies frequently were performed in succession, and second ceremonies were carried out in 46% (15/33) of the cases.

A brief description of the *sip mmien* is presented here because it explains the important role of ancestors in illness causation and curing and the need to perform placating ceremonies to ensure good health. During *sip mmien* ceremonies, ancestor spirits are called to protect living family members, or evil spirits are called to appease them. These ceremonies are an essential part of Mien traditional religion. Some *sip mmien* ceremonies require a written record of the family's genealogy for as many as ten generations. Common ceremonies can be conducted by the male head of household, but Mien specialists are needed to perform the more complicated ones. Family members may watch the ceremony but do not have an active role. The ceremonies are usually conducted midmorning and are conducted annually for the family, for the birthday of all household members, and for illnesses, distress, and so forth. A *sip mmien* ceremony usually involves offering an animal to the ancestor spirits. Only domesticated animals can be used as offerings. A chicken is used for minor ceremonies, a pig for more important occasions, and occasionally a cow is offered. The killing of the animal is not ritualized, and large animals are often slaughtered at farms or packing houses before being purchased by the Mien. The manner of butchering is important, however, and large animals must be carefully dismembered to "reassemble" the animal temporarily at the location of the *sip mmien* ritual. After the ceremony, the animal is cooked and eaten by the household.

Phat. Phat is another form of Mien traditional healing in which ancestor spirits are invoked. *Phat* differs from *sip mmien* in several important ways: *Phat* calls the ancestor spirits or the spirit master of the healer rather than of the afflicted; it is performed only by priests versed in the ceremony. *Phat* is now used only for healing and other beneficial purposes, although elder Mien recall some practitioners casting evil spells in Laos. For healing purposes among the study participants, *phat* was performed for 6% (10/174) of reported illnesses. *Phat* was used primarily for respiratory symptoms and also to treat the child who had soul fright. Traditionally *phat* also is used for physical illnesses such as sprains or broken bones.

Christian Mien healing practices. Mien who have converted to Christianity do not use *phat* or *sip mmien* because these ceremonies call on Mien ancestor spirits. Christian Mien are unable to call the ancestors because they no longer have the written records with the necessary information to perform these ceremonies. Christian Mien ministers explained that conversion to Christianity requires a family to destroy the written family records and the paraphernalia required for *sip mmien* ceremonies. The loss of these items makes it almost impossible for a family to convert back to Mien traditional religion.

Altogether, 28% of study participants were Christian. Of this group, 14 people experienced 24% of the illnesses. Christian prayer was offered for 20% of all illnesses and for 83% (35/42) of illnesses among Christians. Christian prayer was both a social and private intervention. People from the church assisted with the prayers in 63% of the cases. This assistance was offered at the church for half of the cases, at private homes (5/22), and in both home and church (6/22). Figure 1 presents the treatment choices available to Mien depending on whether the cause of illness is perceived as being physical or spiritual.

Multiple treatment practices. Mien used more than one therapy for most diseases, including a combination of Western medical, Mien traditional herbal and *sar* treatments, and spiritual rituals. The study participants did not have an ideal

treatment for all illnesses. Even the elder priests of Mien traditional religion thought that both Western medical and traditional practices were needed.

The largest category of single treatment for all illnesses comprised visits to a Western physician or the use of American medication (prescription or over-the-counter drugs). Almost half of these visits were for respiratory illnesses. Western treatment was used in combination with Christian or Mien religious rituals (*sip mmien* or *phat*) and Mien physical treatments (*sar* or the use of herbal medicines) for 72% of total treatments. Traditional methods (*sip mmien, phat, sar,* or herbal medicine) were used exclusively to treat only 10% of illnesses. Of the total number of illnesses, 9% had no reported treatment. There was wide variation by symptom in type of treatment used.

Several factors influence the choice between traditional and Western self-care or professional care. Most Mien reported little philosophic difference between Western medical

		Illness Cause	
		Physical	Spiritual
Treatment Type	Physical	Physician *Sar* Herbal	None
	Spiritual	Prayer*	*Sip mmien* *Phat* Prayer*

Figure 1.—The diagram shows the Mien illness classification and treatment scheme. *Prayer is used if the patient is Christian.

care and the Mien traditional interventions of herbal medication or *sar.* Mien believe that both Western and Mien methods of treatment address physical aspects of illness. When spiritual causes for illness are suspected, this aspect must be addressed separately. Determining spiritual causation of a given illness has less to do with specific symptoms than with recent experiences or dreams. The following case demonstrates the integration of traditional and Western medicine treatments.

Case Example: Illness with spiritual causation treated with multiple methods. A young woman had dysuria and increased frequency of urination develop, both signs of an infection of the urinary bladder. When she was waiting for a medical evaluation in the emergency department of a local hospital, she recalled recently reading a letter sent from Thailand about deceased relatives. She suspected that reading this letter caused the spirits of relatives to become unhappy and led to her symptoms. She phoned her father from the emergency department, who agreed with this assessment. He then performed a healing ceremony at home on his daughter's behalf while she waited for treatment at the hospital. The woman waited for the medical evaluation and the prescription of antibiotics, explaining that even if the spiritual cause of the ailment was placated, the physical infection was best treated by oral antibiotics. After taking the prescribed medication, she reported a rapid resolution of the symptoms. She attributed treatment success to the efforts of both the physician and her father.

Discussion and Conclusion

The findings show that the Mien use medical services from many sources. Both private and public health care providers are used, as well as traditional healing practices. The ease with which Mien combine multiple healing systems results from their explanation of disease causation. In Western medicine, a differential diagnosis is based on symptoms described by the patient and signs found by the health professional's examination. Mien take a different approach to assessing illness causation. They believe that illness is a state of physical dysfunction, and the origin of this condition must first be determined before undertaking treatment. The emphasis is on *what* caused the symptom and *why* it started, not on an identification or diagnosis of the condition itself. Several methods are used for determining illness causation, including patient introspection, the recollection of dreams and events, and consultation with a senior family member or a priest. For more complicated conditions, religious ceremonies may be performed to invoke and query the patient's ancestors about the possibility of angry spirits causing the illness. All cases of spiritual causation must first be addressed by the patient and family to ensure a resolution of the symptoms. If there are no indications of spiritual involvement, illnesses may be treated only with physical remedies such as medical interventions or *sar.* Western and traditional remedies may be used at the same time, as in the above case example of the woman with dysuria.

A key factor in determining treatment choice for the Mien is their perception of illness causation. Such information, however, is often unavailable to Western health care practitioners, who may be unaware that the patient's explanatory model is an integral component to patient compliance. In the case discussed, only a short course of antibiotic treatment was needed. Sensitivity to patients' belief about the cause of illness is particularly important for chronic illnesses (such as hypertension or diabetes mellitus) and acute illnesses requiring intervention such as an operation, transfusion, or organ transplantation for health practitioners to communicate effectively with patients about the risks and benefits of prescribed treatments.

The Mien community's easy access to prescription drugs over the counter (OTC) raises concern. For example, penicillin was self-prescribed for such common conditions as colds and heartburn. Mien patients were unaware of the risk in taking these medications and frequently shared medication among household members. Although physicians and nurses are aware that over-the-counter drugs can be associated with side effects and serious reactions, it is important to recognize that Mien and other Southeast Asians may have access to a wider variety of OTC products than other patients. This suggests that health professionals need to take careful medication histories, in addition to supporting the medical recommendation that they request patients bring in all medicines for review during visits. Because the pharmaceutical industry is unregulated in many developing countries, the use of OTC medication without consulting a physician or pharmacist is common. For Mien and other immigrant groups, the use of OTC medication, therefore, represents another example of combining traditional and modern health behavior.

Economic pressures shape behavior. Choosing Western medical care did not place Mien at financial risk because most Mien have Medi-Cal health insurance coverage, which eliminates out-of-pocket expenses. Provider choices were limited, however, because of Medi-Cal's low reimbursement to private physicians. Other reported barriers to care included the long waiting time at public clinics, geographic

distance and inaccessibility by public transportation, and limited access to trained medical interpreters at health clinics.[16]

Barriers were also encountered in seeking traditional medical treatments. As discussed earlier, herbal products are not readily available in the US, which contributes to the high price and paucity of many substances required for herbal treatments. Traditional ceremonies also may involve a substantial investment of time and money. If the religious head of household is not skilled in the required ceremony, a priest with adequate skill must be located and compensated. The animal offering must be purchased. A live chicken is not expensive, but a pig may cost more than $200. Traditional ceremonies involve a large investment of time and effort. A ceremony must be scheduled at the convenience of the priest; the animal to be slaughtered must be located, obtained, butchered properly, and transported; and the home and food must be prepared for the ceremony. Just as the costly nature of finding a physician who will accept Medi-Cal limits the use of Western medical practices, the costly nature of some traditional ceremonies limits their use.

This study demonstrates that Mien have not abandoned traditional methods of healing, although they have accepted Western medical care, consult physicians, and use modern pharmaceuticals simultaneously. Most medical symptoms were treated with Western medical care or with both Western and traditional care, and only 6% of all reported illnesses were treated solely with traditional methods. Mien incorporation of Western causes into traditional illness models has not required the replacement of beliefs. Mien do distinguish between "physical" and "spiritual" causes of illness but integrate the treatment of illnesses with these dual causations.

Health care professionals in Richmond perceived long-term Mien refugee patients in the 1980s to be more insular and more likely to use traditional treatments than other Southeast Asians. In contrast, Brainard and Zaharlick's cross-sectional study of long-term refugees in Ohio found that ethnic or lowland Lao who had access to physicians before migration eschewed traditional treatments in favor of Western medical care in the United States.[7] Such contrasts in study findings support the argument that cultural and historical factors play a significant role in how people choose among healing options in a new country and may influence the interaction between health care professionals and refugee patients. Mien are but one of many Southeast Asian refugee groups who share similar practices, although most beliefs and practices are culture specific.[18] Health practitioners and planners, therefore, need to be sensitive to the specific cultural issues of each ethnic group they serve and not make sweeping generalizations.

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Cross-cultural Medicine
A Decade Later

The Effect of Values and Culture on Life-Support Decisions

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Withdrawing life support is always difficult. When patients and health professionals are from different ethnic backgrounds, value systems that form the basis for such decisions may conflict. Many cultural groups do not place the same emphasis on patient autonomy and self-determination that Western society does and find the idea of terminating life support offensive. Although physicians should never assume patients will respond in a particular way because of their ethnic background, issues of life support should be discussed in a culturally sensitive way. African-American, Chinese, Jewish, Iranian, Filipino, Mexican-American, and Korean patients were surveyed about their views on life support. The findings reported here, although not meant to be definitive, should add to health professionals' understanding about diverse beliefs around life-and-death issues. By becoming aware of this diversity of beliefs, health professionals can avoid the damage to the physician-patient relationship caused by conflicting value systems.

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Many challenges to the physician-patient relationship occur in the period around a patient's death. Even in the best of circumstances, discussing starting and stopping life support is emotionally demanding. Poor communication between the physician and the patient or the patient's family can turn this situation into a nightmare. The psychological damage cannot be undone and may cloud the last memories the family has of the patient. Similarly, the physician will always carry the knowledge that the situation might have been handled better.

Instances of poor communication can occur if the cultural values of the health care professional and the patient are different, and each is unaware of the reasons underlying the other's behavior or viewpoint. This frequently leads to frustration, anger, and stereotyping. The problem is especially important when life-support measures are being discussed, as cultural patterns have great strength and influence in the period around a death.[1] It is unacceptable for a health professional to be ignorant or insensitive to the cultural beliefs of a dying patient.

In this article I address the response patterns of several different cultural groups when issues of life support are discussed and explore some reasons for their reactions. These are preliminary results from a survey of 230 patients at a county facility in Los Angeles, conducted to determine whether important differences existed in the views held by members of various cultural groups toward life support. Patients were given a self-administered questionnaire in either English or their native language and were asked to indicate their age, sex, ethnic self-identity, religion, duration of residence in the United States, and level of education. They were given clinical scenarios with various degrees of illness and asked to record what they would do about life-support issues in those situations. The survey did not address reasons behind the chosen action, but, on occasion, patients volunteered this information. A literature review of pertinent sociologic and anthropologic work expanded understanding of the reasons for various responses.

Table 1 shows the large differences among the various groups with respect to starting or stopping life support. The following discussion examines reasons for these differences, using cases from actual clinical situations.

General Considerations

It is not ethnicity per se but the social experiences of different groups that help shape particular cultural organization and value systems. These systems undergo constant, although sometimes slow, change as the social experiences of groups vary. Furthermore, all cultures are composed of individuals and, thus, intracultural variation can be as great as, or sometimes even greater than, intercultural variation.

I present this discussion to help physicians understand why patients might react in the way described, especially when such behavior is different from the physicians' expectations. I do *not* imply that any single member of an ethnic group will respond in the specific way or for the particular reasons mentioned here. To assume that a patient will react in a particular way can be as detrimental to the physician-patient relationship as ignoring the fact that differences exist among patients. Patients should always be treated as individuals first and members of a cultural group or groups second.

Religion is referred to here for several reasons. Religion is often important in shaping values and the moral fiber of societies and thus can help explain differing views toward

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death. In addition, often even persons who are not active in any religion revert to their religious roots when faced with death.[2]

The patients surveyed here were of low socioeconomic status, a class that frequently retains overt indications of traditional cultural values longer than higher socioeconomic classes.[3] The behaviors surrounding death are among the most resistant to change of any cultural or subcultural pattern.[4] Thus, in times of crisis, patients may return to cultural and religious traditions regardless of their socioeconomic status.

Iranians

Case Example

The patient, a 17-year-old Iranian girl, had a long history of diabetes mellitus with numerous episodes of ketoacidosis. On the day of admission, she was found unconscious. When the paramedics arrived she was asystolic, but a cardiac rhythm was restored en route to the emergency department. She was admitted to the intensive care unit (ICU) on full ventilatory support. On evaluation she was found to be brain dead. The family was informed of the diagnosis and the fact that legally she was dead. They objected to removing the ventilator and insisted on many unnecessary medical procedures. They remained in the ICU most of the time, interfering with the care of other patients. The physicians felt that the family was being unreasonable and inappropriate. On the second day of admission when the family was not present, life support was stopped. When the patient's parents found out what had happened, they became irate and refused to leave the ICU. The attending physician talked to them for a few minutes, became irritated, and left. The resident left in tears when the family told her that she had "murdered" the patient.

Discussion

Iranian patients are usually opposed to stopping life support in any situation. There appears to be little difference in the responses of the Muslims and the Christians in the study group, thus indicating that the trend was based in culture, not religion. Because, however, religious values have a tremendous influence on societal norms, and the predominant moral code of Iran is based on Islamic traditions, those will be discussed.

Life and death are viewed as controlled by God.[5,6] All persons are entrusted with their body, and it is their moral duty to seek medical help when needed. The right to die is not recognized.[7] Because only God can decide when someone

TABLE 1.—*Percentage of Respondents (n=230), by Ethnic Group, Who Agreed to Statements About Starting or Stopping Life Support in Hopeless or Terminal Situations**

Ethnic Group	*Average Age, yr*	*% Male*	*Start Life Support? (%)*	*Stop Life Support? (%)*
African American, n=30	38.6	40	Agree (60)	Disagree (40)
Chinese, n=17	35.1	53	Equivocal (53)	Agree (65)
Filipino, n=28	28.4	32	Strongly agree (80)	Strongly disagree (14)
Iranian, n=25	43.7	48	Strongly agree (84)	Disagree (24)
Jewish, n=27	40.1	70	Strongly disagree (13)	Strongly agree (90)
Korean, n=23	42.3	44	Agree (74)	Disagree (30)
Mexican American, n=37	38.1	35	Equivocal (53)	Equivocal (49)
Reference group, n=43†	36.7	51	Strongly disagree (17)	Agree (71)

*Respondents were given 8 different clinical scenarios and told to pretend they were dealing with the situation described. The respondents were asked to indicate what their decision would be in each case. Four of the situations dealt with starting life support, and the other four raised the issue of stopping life support. The hypothetical patients described in the survey were of both sexes and covered a wide age range. The responses of each ethnic group were divided as follows:

Strongly agree ..... >80% of the responses agreed with the statement
Agree..... 60% to 80% of the responses were in agreement with the statement
Equivocal..... 40% to 60% of the responses were in agreement with the statement
Disagree..... 20% to 40% of the responses were in agreement with the statement
Strongly disagree ..... <20% of the responses were in agreement with the statement

Sample questions

CASE 1. Your 8-year-old daughter, Amy, was healthy until last night, when she was hit by a car. She suffered severe brain damage. The doctors, including a specialist, believe that she will never talk or walk again but she will feel pain. She will always need a breathing machine to keep her alive and will need to be fed by a tube in her stomach. The doctors want to know whether you want to keep Amy on the breathing machine (ventilator) or if you would like it turned off. What would your decision be?

☐ Turn off the machine and let Amy die.
☐ Keep the machine on and keep Amy alive.

CASE 2. Your mother, Guadalupe, has had diabetes and high blood pressure for 15 years. She has had several strokes (blood clots in the brain) but is still functional. Guadalupe has told you several times that she never would want to be kept alive by artificial means. Last night, Guadalupe had a massive stroke and was taken to the hospital. The only thing that is keeping her alive is a breathing machine. Would you turn off the machine?

☐ Yes, I would want the doctors to turn off the machine (Guadalupe would die).
☐ No, leave the machine on.

CASE 3. Your father, Peter, is 64 years old. Over the past year he has lost a lot of weight and has been coughing all the time. Two months ago he was told that he had a cancer in his lung that was not treatable. Since then, he has been in constant pain and has been unable to sleep. Last night, your father developed difficulty breathing and was taken to the hospital. The doctors found that his lungs had filled up with water and that the tumor had spread to his brain. He is no longer able to speak, and this will probably not improve. The doctors state that Peter will die the next day, unless he is put on a breathing machine (ventilator) to keep him alive. Even if the ventilator is used, the doctors say that Peter will die in the next few weeks. The doctor wants to know whether you want your father put on the ventilator. What would you do?

☐ Put Peter on the ventilator.
☐ Not put Peter on the ventilator.

†Reference group was composed of all US-born persons who described themselves as white, Anglo, or Caucasian and whose religion was listed as Catholic, Protestant, or none.

will die and all are mandated to seek medical attention, life support is viewed as an obligation, not an option. Although stopping supportive measures is thought to be "playing God," starting these measures is not; instituting life support is an appropriate use of the "gift" of medical technology that has been given to humanity. Thus, to argue with Iranian patients or their families that to start therapy is also interfering with the will of God carries little moral validity.

The opposition to stopping life support holds true even if a patient is in considerable pain. Long-term suffering presents an opportunity to show courage and faith in God,[8] and taking a life to relieve suffering is forbidden.[6] Individual duress is acceptable if it obviates the societal duress of going against moral standards.[5]

Of note, these rules do not necessarily hold in the case of a defective newborn. Some people believe that evil spirits entered the child, and it is no longer human.[9] In these cases it might be permissible to withhold support, including nutrition.

Initiating a discussion of the issues of life support might anger a patient or family. This is based on the conviction that to tell a patient that there is no hope may hasten the dying process and is thus considered inappropriate and insensitive.[10] Given the necessity of obtaining informed consent in the United States, however, some form of dialogue about the terminal nature of a patient's disease is usually necessary. The manner in which such discussion is initiated is important. In Iranian culture it is rude to go directly to the point.[10] The physician should approach the subject slowly, first engaging in small talk. The family dynamics should also be investigated. If a patient is female, she may be under the guardianship of a male family member.[11] The patient's autonomy may not be honored if her decision is not in agreement with her husband's or father's.

In general, the concept of options and patient autonomy is foreign to traditional Iranian culture.[10] Patients are not used to being asked to make choices and may delay doing so. The health care team may become impatient with the patient or family because they "cannot make up their minds" when, in fact, the patient is expecting the physician to make the decisions regarding care.

Other factors can affect decisions about supportive measures in Iranian patients:

- The family's definition of death needs to be considered. In the case discussed here, the family felt that their daughter was still alive because she had a heartbeat and her skin was warm. Thus, to them, removing the ventilator was tantamount to murder.
- In Iran and in many other Middle Eastern countries, the family is expected to be demanding.[10] This shows concern for their family member. This is why the patient's family in this case stayed in the ICU and was so insistent on a wide range of medical care. Not to have done so would have indicated that they did not care about their daughter. Although physicians often become frustrated with this demanding behavior, to understand the reasons behind it may help alleviate some of the friction it causes.
- If a decision is made to stop life support in a Muslim patient, certain customs should be observed. The family should be allowed to stay in the room and recite the Koran *(Qur'an)* so that these are the last words the patient hears.[2,11] In addition, family members should be allowed to move the bed so that the patient is facing Mecca when he or she dies. Finally, when a Muslim dies, a non-Muslim is not supposed to touch the body, so gloves should be worn.[12,13]

Korean Americans

Case Example

The patient, a 54-year-old Korean man, was admitted to the hospital with idiopathic pulmonary fibrosis. His condition deteriorated rapidly, and it was clear that death would occur within the next week. His physicians wanted to issue a do-not-resuscitate order, but his family disagreed, insisting that everything be done to keep him alive until arrangements could be made to fly him to Korea. The house staff thought that the family was unreasonable about the patient's prognosis and was causing him undue suffering. The family did not understand why the physicians were being so insensitive.

Discussion

There is little in the medical literature about Koreans and their views toward ethical issues in medicine, especially life support. The following factors are important, however: First, most Koreans are religious, with Buddhism and Protestantism exerting the greatest influence.[14-16] Many Koreans interpret stopping life support as interfering with God's will, although starting such measures is not. There is also still a strong Taoist influence in Korea, which places a great value on longevity.[14]

Another, perhaps more important, issue is that of filial piety, or loyalty to one's parents. In Korea as in many Asian countries, elders are to be respected and cared for.[14,15,17,18] Children, especially the oldest son, owe their life to their parents. They are responsible for the parents and must preserve their lives at all cost. To agree to stopping life support, even if this is a parent's desire, may dishonor the family member in the eyes of relatives or the community. How people's actions are viewed by others is important.[19]

In addition to respect for elders, there is also a traditional concept of obedience to the male head of the family. This tradition has been shown to be still present in Korean-American families,[20(p115)] and physicians may find that the father or husband makes life-support decisions about all family members.

Traditional values dictate that a patient die at home.[18] Thus, in this case example, the patient's family was aware of the terminal nature of his illness but wanted to keep him alive long enough to get him back to Korea. The fact that he would die en route was not important to them; the action was more important and preserved their honor.

Chinese Americans

Case Example

The patient, a 69-year-old Chinese-American woman, was admitted with complete right hemiparesis and aphasia due to a stroke. She had a history of several previous infarcts, with a resulting dementia. A feeding tube was placed, but the patient repeatedly pulled it out. The family was asked to consent to a gastrostomy tube for feeding. They refused and, in addition, asked that all intravenous hydration be discontinued. Because of a question the patient's son had asked about the cost of nursing homes, the intern was certain that the family wanted the patient to die so they would not have to spend their potential inheritance on her care. The intern wanted to get a court order for the gastrostomy tube.

Discussion

Literature about traditional Chinese culture provides some explanations for the bipolar trend—both to stop life support and to believe strongly that all measures should be continued.* For centuries the moral outlook of China has been shaped by Confucianism, Taoism, Buddhism, and, more recently, Marxism. This has led to an ethical perspective that is strongly virtue oriented.[21,22] What is valued is not life itself but living in an ideal way. Taoism advocates nonaction and allowing things to be, and Buddhism emphasizes the transitoriness of life.[23] ("Death is only the vanishing of the human body, the true body exists forever."[24(p13)]) These viewpoints, combined with the concept of *Ren* (benevolence, kindheartedness, humaneness),[25] lead many patients or their families to the belief that nature should be allowed to take its course, especially when a patient is suffering. Chinese philosophy has long included the right to choose death,[26] and there is evidence that most Chinese approve of passive euthanasia.[27]

In addition, each person is seen as part of the whole community, and individual actions must always take into consideration the effects on society.[22,28] Thus, economic factors become an issue.[29] If life support is a financial burden on the family, the patient or family is likely to request that it be stopped.[30] An explanation for this view can be found in the teachings of Buddha: The principles of justice and compassion are central.[31] Justice requires an appropriate distribution of health care resources. Compassion encompasses justice. Thus, a patient who decides to forgo life-support measures so the family does not suffer, either emotionally or financially, is performing an act of compassion, which is highly valued.

Opposed to this is a traditional Chinese view that life should be valued and preserved at all costs and that physicians should do their best to save lives.[27,30] This is partially based on the first Buddhist precept that prohibits killing, even when a person is suffering from a painful and incurable disease.[30] There is also the concern that to stop life support is to interfere with a person's *karma*—the idea that suffering is the result of some past deed and if the karma is not "worked out" in this life, the patient will be forced to suffer again in the next life.[31] Yet another factor involved is the concept of filial piety,[25,27,30,32] discussed earlier.

Orthodox and Non-Orthodox Jews

Case Example

The patient, a 34-year-old man with alcoholic liver disease, was admitted with his tenth episode of massive hematemesis over the past six months. During his previous admission 14 days before, the patient received 110 units of fresh frozen plasma and 68 units of red cells. On admission the patient had alcohol on his breath. After 24 hours he was still requiring constant transfusions. The attending physician decided to stop all blood products. On hearing this, the Jewish intern caring for the patient vehemently argued that such action was wrong and then left the ICU extremely upset.

Discussion

When raising the issue of life support with Jewish patients, identifying which sect they are associated with is essential. There is a great dichotomy between the views of Orthodox and non-Orthodox Jews. Both views are discussed here.

Traditional Orthodox teachings are firmly in favor of continuing life support. An Orthodox patient may become upset at a health care team for even bringing up the subject of stopping life-support measures. Reasons for this can be found in Orthodox teachings that take a strong prolife stance. Life is sacred and is to be preserved whenever possible.[33-35] Thus, it is mandatory to maintain one's health[35] and to seek health care when needed.[34] In addition, the traditional interpretation of the Bible says that physicians are mandated to save life when able[34,35] and definitely should not assist a patient's death. (Someone who even closes the eyes of a dying person while the soul is departing is classified as a murderer.[36]) So strong is the requirement to preserve life that the risk of a loss of life supercedes most laws of the Sabbath.[34] Every life is of infinite worth, and even one moment of life is to be valued as if it were a month or a year. The sanctity of life is more important than its quality. Furthermore, physicians cannot make a judgment about another person's quality of life because life may have meaning under all conditions, even when the suffering is immense.[37] Thus, conservative interpretations of Jewish moral standards command that patients seek life-support measures and compel physicians to provide them. Although autonomy is valued, wishes that do not comply with these moral standards are not to be honored.[33]

On discussing his feelings, the intern in this case indicated that he was Orthodox and that he believed that not giving blood to this patient was wrong. This is an important case example because it shows how conflicts due to differences in values do not always come from patients. Physicians, too, carry value systems that relate to their past experiences, upbringing, and ethnic identity. Health care professionals need to be aware of their own biases when dealing with these potentially difficult situations.

The views explored here are not necessarily held by non-Orthodox Jews. Possible reasons for this include that Judaism does not glorify suffering by assigning it the redeeming features that other faiths do. No one is required to withstand intractable pain to preserve life.[38] Judaism is committed to use all available resources to alleviate suffering to every extent possible.[39] Thus, pain should be treated. Prolonging the dying process is also prohibited.[34] Exactly what constitutes this dying process is unclear, but traditionally a person who is dying (a *goses*) is one who will not live more than 72 hours.[35] In this situation, it is permissible to stop life support because it is only prolonging the dying process. Another reason for being against life-prolonging measures is that Jews do not have the same belief in an afterlife or reincarnation that other faiths do. There is the feeling that "when it's over, it's over," and there is no point in prolonging futile care.

African Americans

Case Example

The patient, a 32-year-old African-American man, was admitted after receiving a stab wound to the heart. He had a cardiac arrest in the emergency department, suffering severe brain damage. A month later the patient had no notable return of cognitive function, although he was responsive to pain. He had continuous fevers, though no source of infection was found. The ICU team wished to issue a do-not-resuscitate order, stop antibiotic therapy, and transfer him to the

*See also J. H. Muller and B. Desmond, "Ethical Dilemmas in a Cross-cultural Context—A Chinese Example," on pages 323-327 of this issue.

general medical ward. The patient's wife disagreed and threatened to sue the hospital if these plans were carried out.

Discussion

An exploration of the views that African Americans hold toward do-not-resuscitate orders and life support is especially important because of the higher prevalence in the African-American community (than in the general population) of conditions likely to result in the need for a discussion of such issues. Overall, African Americans have higher incidences of cancer, accidents, the acquired immunodeficiency syndrome, hypertension, diabetes mellitus, and low-birth-weight babies[40-47]; they also have less access to needed primary health care.[48]

As is the case with all groups, African Americans cannot be lumped together, as past experiences, religion, and politics are extremely varied. Because of centuries of slavery and racism, their experiences in the United States are dissimilar from all other groups. Patients who recently arrived in the United States from Africa cannot be included in this group, as they have different experiences and medical belief systems.

Although the literature is sparse, there is some support for the finding that African-American patients are more likely to want life-support measures to be continued. Port and co-workers found fewer deaths due to the termination of dialysis in African-American patients than in whites.[49]

Several factors may influence decisions about life-support options. First, African Americans tend to be more religious and more devout than whites.[50] Many patients said that they would continue all measures until the end because it "is wrong" to stop and miracles are always possible. Patients said that they would feel enormous guilt about stopping support. This relates to both strong religious convictions and the observation that, in general, African Americans highly value their elders, long life (regardless of suffering), and the will to survive.[51-54] A physician's statement that the situation is hopeless may not be adequate: only God knows for sure. This may represent a distrust of the medical community rather than strictly religious conviction.

In addition, there are still problems with racism in the medical establishment. It has been shown that African-American patients receive less intense care[55] and are more likely to be negatively stereotyped than other patients.[56] These issues, combined with the perception of some African-American patients that their hospital stay was too short and the care less than satisfactory,[57] may lead to concerns that life support was stopped prematurely because of the patient's race.

Filipino Americans

Case Example

The patient, a 44-year-old Filipino woman with metastatic breast cancer, was admitted with shortness of breath. On admission the house staff discussed the possibility of a do-not-resuscitate order with her. She agreed. Later, while the attending physician was examining the patient with her family in the room, he again brought up the subject of a do-not-resuscitate order. This time she denied that it was what she wanted. On leaving the room, the attending physician expressed displeasure with the resident who had initiated the order "without the patient's consent."

Discussion

The Republic of the Philippines is a diverse nation comprising more than 7,000 islands and with a culture that has been influenced by many countries and religions.[58] Compounding this diversity is the fact that there have been several different waves of immigration to the United States from the Philippines, with each group having unique experiences and backgrounds that would influence their belief systems. Despite this variety, most Filipino patients are apparently opposed to stopping life support.

Many of the Filipinos who have immigrated to the United States are Catholic[59] and believe that patients or physicians should not interfere with God's plan. The Catholic Church abhors "suicide" for any reason,[60] and it is morally wrong to encourage death with any action or omission. Thus, religious conviction is a major reason for continuing life support. Respect for elders is also important, as with Korean and Chinese patients.

The Filipino family greatly influences patients' decisions about health care.[58] Harmony is valued, and personal needs are subjugated to keeping group harmony. Thus, in this case, the patient actually did want the do-not-resuscitate order to be written and did not want life-support measures started. Her family objected, however, and because outright disagreement was to be avoided, she changed her mind.

The perceived cause of a patient's illness can also be a factor in decisions about supportive care. For example, for some Filipinos, illness may be attributed to a punishment from God,[57] and thus it would not be appropriate to interfere. Others believe that people die because they have offended or are possessed by a spirit, a belief that is common throughout Southeast Asia.[61,62] Patients or families may be reluctant to stop life support before the causative agent has been addressed. For example, the brother of a patient thought that she became ill because she swept dirt on a spirit who was walking by, thus offending the spirit. He believed that if the patient apologized enough she would get better, so stopping the ventilator was not appropriate.

Mexican Americans

Case Example

The patient, a 43-year-old Mexican-American woman, was admitted with known metastatic breast cancer. On admission she said she wanted no heroic measures done. Over the next 24 hours her condition rapidly deteriorated, and she became comatose with imminent respiratory arrest. The issue of a do-not-resuscitate order was discussed with the patient's children. They were aware of her wishes but insisted that she be intubated, at least until their father was able to come from Mexico.

Discussion

Mexicans have a rich heritage, with their present culture influenced by indigenous native traditions as well as customs and beliefs imported from Spain and Africa. Mexican Americans have had these traditions modified further by the dominant American culture. This has led to a unique and diversified culture that only partially resembles those of other Spanish-speaking countries. Although Mexican Americans are the largest group of Latino patients,[7] a substantial number of persons come from other Hispanic countries. The following comments should not be assumed to relate to these other groups.

Mexican Americans' beliefs about illness causation are important in determining their views about life support. Health is a gift from God, and ill health, including accidents, may be due to a punishment from God or the saints.* The suffering incurred is part of God's plan and should not be interfered with. Conversely, a patient may believe that the illness is caused by evil spirits or the Devil[67-70] and that a *curandero* (healer) may be able to cure the patient, even when Western medical practices have failed.

Other issues are equally important when discussing life support with Mexican-American patients. First, there is always hope the patient may get better, so to stop life support may cause the Mexican-American family great feelings of guilt. In addition, Mexican Americans believe that enduring sickness is a sign of strength.[70] Some studies suggest that Mexican Americans may have more fear of dying than other ethnic groups.[50] Last, more than 85% of Mexican Americans are Catholic[50] and against anything that hastens death.[71(p282)]

When a patient is terminally ill, the family is involved in all aspects of decision making. The well-being of the family is valued over that of individual members. Traditionally the father or husband is the head of the household,[72,73] and he should make or agree with all decisions. The wife's input is usually influential, however, even when it is not highly visible.

When discussing life support, physicians need to be aware of the concept of courtesy as it pertains to Mexican-American patients. Directly contradicting a physician is considered rude or disrespectful.[67,72] Thus, a physician may think that a patient and the patient's family are in agreement with the plan of action when in fact they are strongly opposed to it. There is also still a strong tendency toward paternalism,[74] and physicians may be expected to make life-support decisions for their patients.

Summary

The frustration that health care professionals experience when treating patients from different ethnic backgrounds can be mitigated by exploring the cultural foundation of the behavior in question. Variants of the factors discussed in this article occur in diverse cultures, although their degree of influence may vary. In addition, people who have identical reactions when confronted with the subject of stopping life support may have entirely different reasons for their behavior. Thus, when discussing do-not-resuscitate orders with patients from any culture, it is best to explore the following issues:

- What do they think about the sanctity of life?
- What is their definition of death?
- What is their religious background, and how active are they currently?
- What do they believe are the causal agents in illness, and how do these relate to the dying process?
- What is the patient's social support system?
- Who makes decisions about matters of importance in the family?

Health care professionals should remember that many patients have immigrated from countries where as much as three fourths of the population does not have access to basic health needs, such as clean drinking water. They have never before faced "high-tech" health care and do not have a clear concept of the implications or consequences of initiating life support. Finally, the concept of patient autonomy that is so highly valued in Western culture, and is the basis of many life-support decisions, is not as important in other cultures.

When faced with life-and-death decisions, all patients draw on a lifetime of experiences for strength and guidance in making decisions. Patients' societal traditions affect their interpretation of past experiences but are not the only factors involved. Each patient must be seen as a person who has a unique belief system, with ethnic background only a part, albeit an important part, of the equation. By discussing life-support issues in a culturally sensitive way, a physician can turn a potentially exasperating experience into an enriching one, with understanding and respect, if not agreement.

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* * *

Contemplating getting back to Barra de Navidad from New York Hospital

In Barra de Navidad they would let me die
like the manta ray who sinks to the sea floor
in a poetic spread-winged design

or that head which dropped to the dust of the village square
with a surprised grimace/grin on its face,
dual mask of tragedy and comedy.

The people of Barra would not understand.
In Barra de Navidad you are either alive or dead
not neither,
bound, probed, cauterized, anaesthetized,
wearing tubes like unpainted Nahuatl arrows.

The white-flecked ceiling turns blue.
I float this steel-rimmed prison-bed
out of sterile air into moisture, breeze and song
4,000 miles southwest to where

death is as simple and unfearsome as the side of that mountain
which invites me to join its red dust,
pain as simple and swift as that hawk who stalks
that fish, that scorpion who stings that leg

each merely another form of that final predator who attacks
when we relax our vigilance.

IRIS LITT©
New York, New York

Cross-cultural Medicine
A Decade Later

Ethical Dilemmas in a Cross-cultural Context
A Chinese Example

JESSICA H. MULLER, PhD, *and* BRIAN DESMOND, MD, *San Francisco, California*

This case was initially presented and discussed at the Family Practice Residency Program Morbidity and Mortality Grand Rounds, San Francisco General Hospital Medical Center, December 12, 1991.

Considerable attention is now being given to ethical conflicts raised by such issues as the disclosure of diagnosis and prognosis, the role of the family in making medical decisions, and the withholding or withdrawing of treatment of terminally ill patients. Already complicated, these issues take on added complexity in contexts where medical professionals and patients have differing cultural beliefs and practices. Ethical dilemmas that develop in multicultural settings have been largely unaddressed. Through the analysis of a case involving the hospital admission and death of a Chinese woman with metastatic lung cancer, we examine some of these dilemmas and their effect on the patient, family, and physicians. Many issues were raised by this case regarding the relationships among ethnic background, bioethics, and medical care.

(Muller JH, Desmond B: Ethical dilemmas in a cross-cultural context—A Chinese example, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:323-327)

Unprecedented advances in medical technology and changes in the social and economic climates of medical practice over the past 20 years have produced challenging ethical and legal questions. Such issues as the disclosure of medical information to patients, the role of surrogates in medical decision making for incompetent patients, and the withdrawal or withholding of life-sustaining treatment of terminally ill patients have attracted the attention of physicians, medical ethicists, attorneys, and policymakers alike.[1]

Despite growing interest in these subjects, comparatively little attention has been paid to ethical dilemmas that emerge in culturally diverse contexts, where conflicts among ethical principles are rendered even more complex by ethnic and language differences.[2-8]* In this article we discuss the ways in which differing cultural values, expectations, and practices shaped the interactions between a team of American physicians and a terminally ill Chinese woman and her family. Focusing on three areas—the telling of "bad news," the withholding of treatment, and the role of the family—we examine several issues: the culture-bound perceptions of both the physicians and the patient and her family, the conflicts that emerged, the attempts made to resolve these conflicts, and the effects on the interactions.

We have not selected this case for analysis because we assume it is representative of all interactions between Chinese families and American physicians. Such a claim would be foolhardy to make in light of the substantial cultural and individual differences that exist among the Chinese who have immigrated to the United States, depending on place of origin, religious and social class affiliation, degree of acculturation, and personal motivations. Rather, we discuss this case because it raises some of the important ethical issues that can emerge during cross-cultural medical encounters.

*See also J. Klessig, "The Effect of Values and Cultures on Life-Support Decisions," on pages 316-322 of this issue.

Case Presentation

Mrs Lee,* a 49-year-old Cantonese-speaking woman, had come from the People's Republic of China to the United States eight years earlier. She lived with her husband and her youngest son, Arnold, age 22; her other children lived nearby. In January 1990 she was seen at an outpatient clinic because of fever, cough, and right-sided chest pain. A presumptive diagnosis of right-sided pneumonia was made, and she was admitted to the family practice inpatient service of a university hospital. Diagnostic studies (Table 1) revealed that her lung infection was due to an obstructing bronchial squamous cell carcinoma. A metastatic workup also revealed lymph node and adrenal gland metastases. She was treated with intravenous antibiotics and palliative radiation therapy.

During her two-week hospital stay, Mrs Lee's children and husband were with her constantly. Neither Mrs Lee nor her husband could speak English. Arnold Lee, perhaps because he spoke English better than his siblings, became the spokesperson for the family and assumed primary responsibility for decisions. He made it clear that he did not wish to discuss his mother's diagnosis with her and that he did not want the physicians to speak to his mother through interpreters. The house staff taking care of Mrs Lee was concerned that because of the family's protectiveness, the patient did not know her diagnosis and was unable to make her own decisions about the type and extent of treatment to receive.

On completing the course of antibiotics, Mrs Lee was

*All of the names in this article are pseudonyms.

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TABLE 1.—*The Course of the Patient's Illness*

Date	*Event*	*Diagnostic Study*	*Results*	*Action*
1/31/90	Patient admitted with presumptive pneumonia	Chest radiograph	Right middle lobe and right lower lobe collapse	IV antibiotic therapy
2/02/90	--	Bronchoscopy	Lesion obstructing right main-stem bronchus; tissue diagnosis of squamous cell carcinoma	Palliative radiation therapy for lung tumor
2/09/90	--	CT scans of chest and abdomen	Large bronchial tumor; peritracheal adenopathy; large adrenal mass	--
2/09/90	Son assumes decision-making responsibility	--	--	--
2/17/90	Patient discharged	--	--	Outpatient clinic follow-up
5/14/90	Increasing back pain	Magnetic resonance imaging	Spinal cord compression; diffuse spinal metastases	Radiation therapy to back
6/--/90	Patient and family continually refuse to discuss DNR order	--	--	--
6/27/90	Patient admitted with altered mental status	CT scan of the head	Multiple brain metastases	Radiation therapy to the head; dexamethasone therapy
6/29/90	Patient discharged	--	--	Acetaminophen with codeine for pain; home oxygen therapy
8/08/90	Family declines hospice care	--	--	--
8/12/90	Patient admitted with SOB, fever, and cough with blood-tinged sputum	Chest radiograph	Diffuse bilateral infiltrates	IV antibiotics, oxygen, diuretics
8/12/90	Physicians decide medical ICU admission not advised	--	--	--
8/13/90	Patient's condition worsens; family reluctantly agrees to DNR order	--	--	--
8/13/90	Son demands intubation	--	--	Request denied
8/14/90	Patient dies	--	--	--

CT = computed tomography, DNR = do not resuscitate, ICU = intensive care unit, IV = intravenous, SOB = shortness of breath

discharged and observed as an outpatient by her primary physician. Knowing her poor prognosis, her physician tried numerous times to discuss a "do-not-resuscitate" (DNR) order and the possibility of foregoing cardiopulmonary resuscitation or other treatment in the event of a cardiac or respiratory arrest. Arnold Lee, who always accompanied his mother to clinic visits and spoke for her, would not allow such a discussion and became agitated whenever the subject was raised. Unclear about what the patient herself wanted, the primary physician became increasingly frustrated at not being able to communicate directly with Mrs Lee and at the family's apparent denial of the implications of the diagnosis.

Over the next four months, Mrs Lee had increasing back pain and decreased strength in her legs. After a magnetic resonance image revealed evidence of diffuse spinal metastases and spinal cord compression, radiation therapy was started to Mrs Lee's back. Toward the end of June she was briefly admitted to the hospital because of altered mental status and weakness. Diagnostic studies revealed multiple brain metastases, requiring further palliative radiation therapy. After discharge Mrs Lee went home, where she used oxygen intermittently and was kept free of pain with acetaminophen with codeine. The primary physician suggested hospice care, which the family declined.

On August 12, 1990, Mrs Lee came to the emergency department with progressive shortness of breath, fever, and cough productive of blood-tinged sputum. On physical examination she appeared ill, had cushingoid habitus, and was in moderate respiratory distress. She was admitted and treated with a regimen of intravenous antibiotics, oxygen therapy, and diuretics. Over the next 48 hours, the patient's condition deteriorated until she became nonresponsive with labored breathing. House staff repeatedly brought up with the family the question of her code status. The family adamantly refused to consider a DNR order and insisted that she receive all possible care. Convinced that the family had unrealistic expectations about the patient's prognosis, the resident and intern became increasingly upset and anxious. They were worried that the invasive interventions required if the patient had to be resuscitated not only would be medically futile but would cause the patient great suffering and indignity. The attending physician concurred with their assessment, wrote a DNR order in the patient's medical record, and informed the patient's husband of this decision. The family reluctantly agreed to the order.

As Mrs Lee's condition worsened, her family became more visibly upset and more vocal in their insistence on extensive and aggressive therapy. When Arnold Lee discovered that ventilator support was a medical intervention that prolonged life, he demanded that his mother be intubated. The resident refused, at which point Arnold insisted on seeing the attending physician. As the attending physician entered the room, Arnold sank to his knees, pleading for him to intubate Mrs Lee. When the physician denied his request, Arnold became even more distraught, accusing the team of physicians of deliberately taking inadequate care of his mother because she was Chinese. Arnold's accusations of racial bias quickly escalated to threats of litigation.

The family's anger, suspicion, and mistrust made the house staff and attending physician question their decisions. Even though they were sure that further treatment of Mrs Lee would be useless, they discussed among themselves the difficulty of determining medical futility and re-examined the diagnostic studies to convince themselves they had reached

the right diagnosis and treatment plan. The attending physician also consulted with the senior resident covering the medical intensive care unit to verify that an admission to that unit was not warranted. In addition, they openly explored the possibility of racial and cultural bias among themselves.

The family remained upset and angry. Arnold Lee called a meeting with the team of physicians during which he continued to insist on heroic measures to prolong his mother's life. After about four hours of discussion, they were interrupted by the patient's daughter, who ran in screaming that her mother in the room next door had stopped breathing. Even though Mrs Lee was dead, the intern asked if she could administer a shot of epinephrine in response to the family's pleas to do something. Attempting to meet some of the wishes of the family, the attending physician, knowing well that it was a futile gesture, agreed. Once it was certain that his mother was dead, Arnold Lee turned to the attending physician and screamed, "Are you happy? You got what you wanted. You murderer!"

Discussion

This case illustrates three areas in which differing cultural beliefs and practices emerged: the telling of bad news, the limiting of treatment, and the role of the family in medical encounters.

The Telling of Bad News

The physicians. Since the time of Hippocrates, physicians have been taught to conceal bad news from patients out of fear that disclosing information of a grave diagnosis would increase anxiety or depression or cause patients to lose hope.[9] Until recently American physicians rarely explicitly discussed "gloomy prognostications" with their patients.[10,11] Increasingly over the past two decades, however, such protectiveness has been viewed as unnecessary. Attitudes about what constitutes benefit and harm have shifted as clinicians came to realize that there was little evidence supporting the view that disclosure harms patients and considerable evidence indicating that patients often benefit from knowing their diagnosis or prognosis.[11]

As principles of contemporary medical ethics have been introduced into medical education and practice, American medicine has come to embrace other moral norms. Medical ethics is a discipline whose origins lie in the branches of Western philosophy and law that give primacy to the individual and to rights of self-determination and privacy. As a consequence, autonomy has become the centerpiece of contemporary theories about how patients and physicians should relate to one another. This principle holds that people have the right to determine their own course of action, even if this means refusing medical treatment.[1,12]

In practice, the disclosure of a life-threatening diagnosis and the ensuing discussions about medical treatment can be difficult.[13] Nevertheless, many physicians now believe that an important part of their role is discussing the "truth" with their patients so the patients can make autonomous, informed decisions about their health care and prepare for their deaths. Direct and honest communication of the facts is considered not only good clinical practice but a "right" to which each patient is entitled. Young physicians are now taught that under most circumstances it would be unethical *not* to talk honestly with their patients about their diagnosis and the realistic consequences of their disease.[14]

In the case presented here, the physicians tried to act in accord with these professional values but perceived their efforts to be largely unsuccessful. Not only did family members not allow house staff to talk directly with Mrs Lee but they appeared to keep information from her and they did not seem to appreciate the gravity of the situation. Baffled and frustrated, the physicians thought that the family was denying the reality of the disease process and its ultimate outcome.

The family. The Lee family appeared to have a set of cultural expectations about the treatment of dying people and the role of "truth telling" in doctor-patient-family communication that differed substantially from those of the physicians. A belief held by many Chinese is that a person is entitled to be treated as a child when ill.[15] Sick adults, like children, deserve "protection." Because a patient is suffering already from the illness, it is unnecessary to make them suffer even more by discussing the reality of the disease. If the patient is gravely ill, the need for protection is perceived as even greater. Among many Asian groups, including the Chinese, to tell someone he or she is dying is not only rude but dangerous.[2,16-19] People fear that openly acknowledging an impending death is like casting a death curse upon the person; it will make the person despair and die even sooner. Thus, to engage in discussions of code status or the possibility of hospice care, interventions that can be seen as explicit preparation for death, is courting bad luck.

"Truth telling" also signifies the withdrawing of hope; it tells patients that their physicians have given up on them and they might as well give up, too. Therefore, it would only be an unthinking, callous practitioner who would even consider engaging in an activity with such dire consequences. This does not mean that the family and patient necessarily remain unaware of the implications of a grave diagnosis. They may well know and accept the reality of the situation but, at the same time, have a tacit understanding born of cultural expectations about how to behave appropriately in such circumstances—that is, not to acknowledge or discuss it openly (B. Koenig, PhD, C. Orona, PhD, A. Davis, PhD, "Cultural Pluralism and Ethical Decision-Making: A Descriptive Study of Patients Facing Life-Threatening Cancer," Division of Medical Anthropology, University of California, San Francisco, unpublished data, 1990).

In an effort to protect Mrs Lee from unnecessary suffering, the Lee family wanted little or no information transmitted to her. The physicians, following their professional imperative of autonomous informed decision making, wanted open and direct discussion. These differing values resulted in a breakdown in communication between the house staff and family and a growing sense of mutual distrust and frustration. When the subject of withholding medical treatment was introduced, the distrust and frustration only increased.

Withholding Treatment

The physicians. Although a wide array of equipment and procedures is now available to prolong the lives of critically ill patients, the use of such interventions is not always indicated. There is widespread agreement among physicians that the possibility of benefits offered by a medical intervention must outweigh its burdens for it to be justified.[20-24] Physicians are not legally or morally obligated to provide therapy that offers no hope of medical benefit and, in the best estimation of the health care professionals, is futile.

In situations where a patient's death is imminent or further treatment is considered futile, it is now common practice to forego life-sustaining treatment. One mechanism for this is the DNR order that, when written in the patient's medical record by the attending physician, bypasses the mandatory use of life-sustaining equipment.[12,25-28] Guidelines for DNR orders stipulate that physicians discuss them with mentally competent patients. With incompetent patients, physicians typically either consult with or obtain permission from the family or guardian. Even when hospitals do not require family consent, physicians are generally expected to make vigorous efforts to achieve consensus. This is especially so in cases where there are conflicting notions of appropriate care or where they feel a DNR order is appropriate for a patient whose family has requested that "everything be done."[29,30]

In keeping with current views, Mrs Lee's physicians made two decisions that would limit the type and extent of treatment they would offer. First, they determined that resuscitation was not appropriate because the chances of her surviving a cardiopulmonary arrest were minimal. On the basis of this assessment, they made repeated and unsuccessful attempts to get agreement from the family about a DNR order. The attending physician, convinced of the futility of possible resuscitation, then wrote a DNR order without the family's agreement. Second, the physicians decided that there was no demonstrable medical benefit to admitting Mrs Lee to the medical intensive care unit and providing ventilator support. They concluded that the burden in pain and suffering far outweighed any benefit a few more hours or days of life might bring.

The family. In contrast to the physicians, the Lee family defined burdens and benefits in terms of the burden of disclosure and the benefit of continued treatment. Throughout the course of the patient's illness, her family was adamantly opposed to any attempt to limit or withhold treatment. When the physicians finally concluded there was nothing more they could do, Arnold Lee asked around to find out which medical interventions could prolong life and demanded that these interventions be used.

The intensity of this response was unusual for Chinese families. Heroic interventions aimed at extending the life of a substantially compromised patient are typically regarded with ambivalence and, especially if the patient is old, are often not appreciated or requested.[16] To understand the reaction of the Lee family, it is important to look at the patient's age and at the role Arnold Lee assumed in the family. A "good death" in Chinese society takes place when a person dies peacefully in old age.[18] Mrs Lee, however, was only 49. Hers was an untimely, "bad" death, making it much harder for her family to accept it. Therefore, when certain interventions that theoretically could sustain life were deliberately withheld, it appeared to Arnold Lee as "murder." As will be described, it then became his duty as family member and son to protect his mother.

The Role of the Family

The physicians. Among Western-trained physicians, family involvement in the health care of a patient is often perceived as directly related to the decision-making capacity of the patient. When patients are unable to make decisions for themselves, physicians turn to relatives, with the assumption that family members will make decisions according to what the patient would have wished or that they will seek to protect the patient's "best interests."[12,30,31] If patients are mentally competent, physicians expect to communicate directly with them. Family members are viewed as intermediaries whose primary role is more to encourage "open" family discussion than to make decisions for patients who are capable of making their own decisions. When families take over the decision-making process, it is considered an infringement of individual rights.[32]

The family. The role of the family in health care is perceived differently in Chinese culture, where primary importance is placed on familial relationships.[19,33] The family is considered an entity that existed before one was born and will exist after one is dead. The accomplishments of individuals are not theirs alone but belong to the family; similarly, shame and misfortune fall on individual members and on their families together. Membership in a family also places on persons certain privileges and obligations. For example, as parents age they expect to receive care from their children. Traditionally, male children learn early, through ideology and strong sanctions, the cultural norm that parents expect to have a son who will be obedient, respectful, and capable of supporting them in their old age.[34]

Within this strong family-centered system, health care decisions are family decisions. In Taiwan and parts of mainland China, for example, decisions about which practitioner to see, when to go, and whether to comply or to change practitioners are typically made within the context of the family or social network.[19] When a person's illness is life-threatening, it is assumed that the practitioner will talk to family members rather than the patient. The family, not the practitioner or the patient, is seen as most responsible for the sick person and decisions about treatment.

Arnold Lee's behavior reflected these traditional familial obligations even though he was acculturated in his language and his knowledge about Western medical interventions. He appeared to see it as his filial duty to do everything possible to protect his mother. By excluding her from discussions with the physicians, he attempted to protect her from emotional stress or loss of hope. By insisting that she receive heroic interventions to prolong her life, he attempted to protect her not only from death but also from a health care system he feared was giving her inadequate care because she was Chinese. Although the motivations for his behavior were unknown, it is possible that to shirk these responsibilities represented "loss of face" for him, a public acknowledgement that he was an inadequate son.

The disparate expectations of the Lee family and the physicians about the nature of obligations assumed by family members led to several ethical dilemmas. For the physicians, it was immoral not to deal directly with the patient when she was still able to make decisions for herself. For the Lees, it was immoral not to deal with the family. Later, when Mrs Lee became incapacitated, the physicians found themselves caught between the wishes of the family that "everything be done" and their own judgment about what would be best for the patient. After painfully reassessing the treatment decisions they had made, they concluded that the interests of the family conflicted with the best interests of the patient. The consequence of these diametrically opposed views was that even after Mrs Lee died, the feelings of hostility and suspicion did not dissipate, leaving family and physicians alike frustrated, confused, and upset.

Conclusions

It is difficult to generalize about cultural representativeness from one Chinese family. In many ways—the family's demand for heroic interventions, the excessive protectiveness of the son, the furious family response—this case is unusual. Nevertheless, it dramatically illustrates some of the issues physicians face in working with Chinese patients and families, such as the extensive family involvement in health care decisions and the importance placed on the nondisclosure of a terminal diagnosis.

The case also raises a few general points about bioethics, ethnicity, and medical care. Current literature on medical ethics focuses on Western biomedicine. It has been dominated by a concern for the ethical implications of developments in medical technology and ethical issues involving physicians and other biomedical professionals. This focus has not been accompanied by a concomitant interest in the ethical implications of cultural pluralism and cultural contact.[6] It is erroneous to assume that the precepts of Western bioethics, such as autonomy, are universally accepted. Serious ethical issues can arise from fundamental contradictions between biomedical perspectives and the norms and values of other cultural groups.

This discussion points to several ways in which physicians working in multicultural communities can attempt to bridge cultural gaps. An important first step is to be sensitive to patients' cultural beliefs and practices. This may require calling for help in interpreting behavior, either from a provider who is from the same ethnic group as the patient or from an expert familiar with the group's language, life-style, and value preferences.[8] Alternatively, co-management with a colleague of the same ethnic group as the patient may reduce cultural misunderstandings. Beyond that, not to fall prey to cultural stereotyping, it is critical that physicians recognize individual differences. Because persons of the same ethnicity can have very different beliefs and practices, it is important to understand the particular circumstances of the patient or family by obtaining information on place of origin, social and economic background, degree of acculturation, and personal expectations concerning health and medical care. Finally, a reflective approach is useful. Physicians should examine their own biases and expectations to understand how these influence their interactions and decision making.

Situations such as the one described are inevitably difficult to handle. When there are strong but different moral imperatives operating, decisions have to be made by balancing often competing values. In this case, increased sensitivity and understanding might not have alleviated the frustration of the health care professionals, but it might have made things more understandable to them and defused the emotional intensity of the situation. For physicians who are struggling with the intricacies of bioethical dilemmas, being sensitive to the cultural beliefs and practices of their patients and yet maintaining their own moral integrity ultimately require a juggling act that is difficult for even the most thoughtful and compassionate professionals to manage.

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- Since 1980, an estimated 75,000 Ethiopian refugees have arrived in the United States
- The 1975 overthrow of Emperor Haile Selassie by a Marxist regime, followed by a period of intense political repression, caused this population movement
- Ethiopia has a highly diverse population

Cross-cultural Medicine
A Decade Later

Medical Disclosure and Refugees
Telling Bad News to Ethiopian Patients

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The strong value in American medical practice placed on the disclosure of terminal illness conflicts with the cultural beliefs of many recent refugees and immigrants to the United States, who often consider frank disclosure inappropriate and insensitive. What a terminally ill person wants to hear and how it is told are embedded in culture. For Ethiopians, "bad news" should be told to a family member or close friend of the patient who will divulge information to the patient at appropriate times and places and in a culturally approved and recognized manner. Being sensitive to patients' worldviews may reduce the frustration and conflict experienced by both refugees and American physicians.

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Until recently, physicians in the United States tended not to disclose the fate of terminally ill patients, even when it was obvious that the patients were going to die.[1] In the past two decades, however, there has been a dramatic change in the policies of American physicians regarding disclosing the prognosis to terminally ill patients.[2-4] The most debated issue in disclosing or withholding information concerns the diagnosis of cancer and the prognosis of imminent death when there are no further treatment options. This shift of American physicians toward disclosure is attributed to underlying changes in the social structure of the US health care system, the demands of patients to know and to decide about their medical care, the legal obligation that requires that patients understand the nature of their disease before consenting to an operation or experimental therapy, and societal questioning of physicians' authority.[3,5]

American physicians' practice of disclosure contrasts with dominant biomedical traditions in other societies.[5] For example, Italian physicians withhold a diagnosis of cancer to sustain hope and protect the patient from bad news. The disclosure of terminal illness is viewed as an important factor in a patient's decline and a cause of further harm.[6,7] In Japan, as a general rule, physicians do not tell patients they have cancer. Even the late Japanese emperor was not told that he had pancreatic cancer.[8] Japanese physicians think that telling patients they have a grave diagnosis will only hasten their death.[8,9]

Disclosure in the American cultural context is essential to obtain consent for treatment, to challenge the disease, and to be in control of the situation. Furthermore, being aware of one's condition affords autonomy and the ability to make decisions and to master one's fate.[7,10] This strong value placed on the practice of open disclosure of terminal illness in the United States conflicts particularly with the cultural beliefs of many of America's recent immigrant and refugee groups, who consider frankness in medical disclosure inappropriate and cruel.[11]

In this article, I explain some Ethiopian cultural reasons for preferring nondisclosure of terminal illness, using a few case examples of Ethiopian patients in the United States. I also suggest some guidelines to minimize conflict between American physicians and their refugee patients. The suggestions are based on my experience as a member of the Ethiopian community and on discussions with Ethiopian patients and families and with American and Ethiopian health care professionals.

Case Examples

Case 1

The patient, a 33-year-old professional married Ethiopian woman, was admitted to a university hospital for surgical exploration for an intractable gastrointestinal disorder. The patient had lived in the United States for more than 15 years, had a college education, and spoke fluent English. Before the patient and the physician agreed to the operation, she had three appropriate tests performed, each with negative results. The exploratory operation revealed, however, that she had stomach cancer that had spread to other organs and was impossible to remove. This finding was disclosed to her husband right after the operation. He was told his wife's prognosis was poor and that she had three to six months to live. The husband requested that the surgeon and her physician not tell the patient at the time and assured them that he would break the news to her at an appropriate time.

Although the husband had requested that his wife not be told, a day after the operation the surgeon went ahead and told her that she had cancer and that it had spread. With this tragic news, the patient fainted. After she recovered from the initial shock, the patient refused to talk further to this physician. The patient described his behavior as "cruel" and "in-

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considerate." She decided she did not want to know the extent of her illness more than she was already told and found an oncologist who was willing to accommodate her wishes. Her entire treatment regimen was then discussed only between her husband and the new physician. Neither her husband nor any other family member encouraged the patient to seek full disclosure. To do so would have taken hope away from her and discouraged her from fighting the illness. Moreover, the larger Ethiopian community would have seen it as an irresponsible and uncaring act on the part of the family members. After a year and a half of treatment, however, having outlived the initial predictions, the patient decided on her own to take part in the clinical discussion of her case and to face the facts about her condition. She was glad that she chose not to know her true condition earlier; if she had known earlier, the magnitude of her illness would have overwhelmed her and discouraged her from fighting the disease.

Case 2

The patient, a 16-year-old Ethiopian girl with an inoperable brain tumor, was admitted to a psychiatric clinic with head pain. The patient was taking several medications for the tumor. Before being referred to the psychiatric clinic, she had been in group therapy at an outpatient clinic where she was described as depressed, needy, and isolated. She did not mingle with the other young people in the group, nor was she willing to engage in discussion, particularly regarding sex. This was perceived by the therapist as abnormal because most American girls her age have a lot to ask and say about the subject. Once admitted, the patient denied that she was depressed and insisted that her major problem was the head pain. Furthermore, her family did not want her to know her diagnosis of brain tumor and had asked her physician not to tell her. Her previous psychiatrist had disregarded this request, however, and had told the patient. When her family discovered this, they interrupted the therapy and changed physicians.

The attending physicians were frustrated, claiming that her family was not honest with her. They also felt that they were blocked from communicating openly with the patient. Because the patient had lived in the United States for about nine years, they felt that she had grown up in this culture and therefore should act like an American teenager.

Case 3

The patient, a 38-year-old married Ethiopian man diagnosed with bone cancer with a poor prognosis, was admitted to a public hospital. The patient knew his diagnosis but was unaware of the poor prognosis. Because he had been in this country for only a couple of years and did not speak English, an Ethiopian interpreter was asked to assist. After a trial of chemotherapy, the cancer was deemed untreatable. The physician involved tried to disclose this fact to the patient through the interpreter, who was asked to tell the patient that there was no more treatment for him and his condition was terminal. The interpreter was able to tell the patient that there was no more treatment for him but could not say to him that his was a terminal case. The patient became distraught and asked the interpreter to tell the physician that he wanted to continue treatment. The interpreter was caught in the middle, being faced with the cultural conflict of telling the patient that he was dying. Finally, the interpreter was able to relate this fact to the patient indirectly.

These case reports show some of the day-to-day conflicts between immigrants and refugees and American health care professionals. Using these examples, I will discuss the Ethiopian core cultural values that are in conflict with American medical practice, particularly in regard to truth telling, the meaning of hope, and death and the role of the family. Readers should keep in mind, however, that variations exist within the Ethiopian immigrant-refugee communities in the United States: urban or rural origin, length of stay in the United States, level of education, gender, age, and religious differences are some of the important factors leading to diversity in this group.

Ethiopian Refugees in the United States

Compared with other immigrant groups, the Ethiopian community in the United States is relatively new and small. The exact size of the community is unknown, with current estimates varying from a low of 50,000 to a high of 75,000.[12] The lack of a reliable census of the Ethiopian population will remain a problem well into the next decade, as Ethiopians were subsumed in the "Other" category for the 1990 census. As a result, Ethiopians face being lost in the large refugee and immigrant population and their needs and concerns going unaddressed.

Before 1974 the Ethiopian community in the United States was small and scattered, with a handful of Ethiopians permanently settled. Of an estimated 3,000 Ethiopians residing at the time in the United States, 95% were students and expected to return to Ethiopia on completing their studies. The other 5% were either diplomats or associated with various international organizations. That year Emperor Haile Selassie was dethroned by a militaristic Marxist regime. Shortly after, from 1976 to 1978, in the course of consolidating political power the self-styled Marxist military government, unwilling to accommodate ideologic differences with other political organizations, unleashed a system of political repression called the "Red Terror" that took thousands of lives. The arrests and indiscriminate executions of suspected members and sympathizers of the opposition and the brutal civil war in Eritrea and Tigray forced many Ethiopians to seek refuge in neighboring and distant countries. Many Ethiopians living in the United States decided to make this country their home, and many more came and settled here as refugees. Most Ethiopian refugees have been in the United States since the 1980s, and many continue to come.[12]

Ethiopia, a country the size of California and Nevada combined, is a multiethnic, multireligious nation with more than 70 distinct languages. Ethiopia is essentially a highland country. The high plateau covers about two thirds of the country, and deep river canyons cutting through the plateau create varying ecologic environments within short distances. Due to the variable topography, there is a marked difference in the climate conditions, which range from being tropical in the canyons to temperate on the plateau, often within a few miles.[13] Despite this tremendous ethnic and geographic diversity, similar core cultural values underlie the behavior of all Ethiopians.

Most Ethiopian immigrants are from an urban background and for the most part live in major metropolitan cities in the United States—Washington, DC; Los Angeles and the San Francisco Bay Area, California; Chicago, Illinois; Boston, Massachusetts; and New York City. Demographic data indicate that there are more men than women, and 70% of the

community members are between ages 18 and 34. In the United States, at least three major Ethiopian languages are spoken among immigrants: Amharic, Tigrigna, and Oromigna. Most Ethiopian immigrants speak English or Amharic, Ethiopia's national language. A number of Ethiopians, however, have difficulty speaking any of these languages.[14] Data on English language skills show that 81% had some skills—ranging from fluent to some English—but 19% had no English skills at all.[12] Ethiopians can be found working across the entire job spectrum, from low-paying "dead-end" jobs to the demanding fields of medicine and "high-tech" electronic or computer engineering. Most, however, work in a variety of service jobs, particularly in restaurants and hotels and as parking lot attendants and taxi drivers.[12]

Ethiopian traditional medicine consists of indigenous magicoreligious practices and beliefs integrated with certain aspects of the Greco-Arabic tradition of medicine.[15-17] Currently in Ethiopia, both traditional Ethiopian medicine and Western cosmopolitan biomedicine are practiced, each being applied to specific illnesses. It is not uncommon to find Ethiopians using both systems of medicine simultaneously.

There are no traditional Ethiopian healers in the United States. This is because the Ethiopian immigrant community consists mostly of young urban people whereas the healing tradition is usually the domain of older people and religious leaders. Traditional medicine in Ethiopia, as in many other countries,[15,18,19] concerns both the prevention and cure of disease. Most Ethiopians place great reliance on religion and God, with prayers being used against illness and misfortune. Family members are important sources of assistance and comfort during periods of serious illness.

Telling Bad News in Ethiopia

The physician in case 1 felt that regardless of the family's wishes, it is a patient's right to know the diagnosis. The patient and her family were upset by the disclosure, however. One family member commented that the patient could have died of the shock from the bad news.

It is vital in Ethiopian culture that to break bad news such as grave illness or the death of a family member, an appropriate time, place, and way be chosen. A sudden shock is to be avoided at all cost, especially when dealing with children, the elderly, and sick people because of the harmful effects this news may have on people with fragile emotional states. The disclosure of bad news is staged, and close friends or family members prepare persons to face disturbing news by leading them to it gradually. The situation is discussed among friends and relatives to decide the appropriate time and the least frightening way of breaking the news. If it is a death or an accident involving a family member, the news is disclosed to close friends before a person is told so that they will be there to provide emotional support. For Ethiopians, it is important how tragic news is communicated to them. Tragic news is not told in the evening, unless it is something that needs immediate attention; even then, breaking the news is staged. For example, a typical way of informing a person of bad news such as the death of a family member who lives out of town is to break the news in the morning, at the person's residence and in the presence of close friends. Friends and relatives stay with the person, keeping him or her company, preparing food, and sometimes even staying overnight. Breaking tragic news in the evening will impose a long, sleepless night and add more hardship on all parties concerned.

For Ethiopians the extended family is the most important institution. Children remain deeply attached to their families and sensitive to the wishes of their parents. Obligations toward the family persist long after children have married and established families of their own.[20] During illness and crisis, Ethiopians rely heavily on family members to help them cope. Therefore, the role of the family and of friends is important for them. Families are responsible for managing the information and the illness experience of a family member during a period of illness. In cases of serious illness, physicians communicate little information to patients. Whatever the diagnosis, they are expected to tell the bad news to a family member first.

A family will judge how and when they want to let a patient know; this may vary with the age, level of understanding, and the emotional and physical condition of the sick person. In case 2, the family felt that a 16-year-old girl was too young and should not be burdened by the news of her impending death. Furthermore, in Ethiopian culture, sex is a private matter and children are socialized never to discuss sexual matters openly. The teenager in case 2 was caught between the expectations of two cultures.

Telling the Truth and the Effect on Hope

All societies seem to recognize the need for hope but differ in understanding the conditions for it. Offering hope is a form of caring that is embedded in a cultural context.[6,7,10] In the North American culture where the values of individualism, autonomy, and self-reliance are important, providing the "naked" truth about illness is seen as a way of giving patients hope. Disclosing all the facts gives patients a sense of control over their illness and allows them to help decide their fate. Furthermore, total possession of such information is a legal right. Diagnostic information regarding one's body and life belongs to the person about whom it refers, not to the family or the physician.[10,21]

In contrast, in traditional societies like Ethiopia, where the family's importance dominates over individual members', any information, including diagnostic facts, belongs to the family. The family then uses the information at its discretion for the benefit of the patient. In such societies, families tend to protect their ill members from knowing the gravity of a situation to maintain hope and the equilibrium of day-to-day living. Not knowing the gravity of a condition allows the patient to hold on to the hope of a cure. In these societies, the physician collaborates with the family in protecting the patient from such bad news.[6,7]

In Ethiopian culture, the patient and healer relationship is paternalistic and protective, and trust is a major component of this relationship. Moreover, Ethiopian traditional medicine, like many other traditional medical practices,[19] is mostly concerned with the act of healing the patient. All the attention of the healer is in the act of diagnosis, to find out who or what caused the illness and to remove the pathogenic agent. Prognosis has no dominance in the medical systems of traditional societies.[15,19] The current physician-patient relationship in Ethiopia is parallel to the relationship with indigenous healers. Ethiopian patients rely on their physicians to cure their illnesses and help them manage their pain. Most of all, they want to be reassured that they will get well. Disclosing a serious diagnosis with a poor prognosis conflicts with the hope for healing.

Moreover, it is taken for granted that physicians' actions

are always for the good of patients. An Ethiopian physician, for example, said that he will tell an Ethiopian patient who has a 40% chance of surviving with treatment that the disease is 100% treatable because Ethiopians seem to do better when reassured. Even if patients find out that what they were told is inconsistent with medical findings, Ethiopian patients are not going to question their physicians' honesty. Physicians' actions will be considered a form of caring. In contrast, Americans will consider this dishonest and may even pursue legal action.

Honesty is the most highly valued character trait in the Ethiopian culture. Truth is socially defined, however. In Ethiopia it is acceptable to employ deception in not wanting to tell a person something that will offend or hurt. In Ethiopian culture deception has its more subtle passive forms—deceiving by omitting the truth rather than committing a falsehood.[20] Furthermore, contrary to the American reliance on an explicit verbal communication of emotion, Ethiopians rely on nonverbal communication. Feelings are expressed by action and behavior; love and concern are rarely expressed verbally. Family members convey their love for each other by being protective of each other's feelings, protecting each other from suffering (emotional and physical), surrounding a person in a time of crisis, providing care, and believing in and encouraging the person to hold on to hope.

Although it appears to outsiders that patients are kept in the dark, in most terminal situations it is apparent that the patients know that death is imminent. After all, no one is more able than patients themselves to judge failing health. Contrary to the American concern of overtly preparing for death,[22] some cultures have a way of getting ready to die that does not have to be verbalized. For Ethiopians, however, preparing for their death does not affect their faith in hope, and any discussion of the impending death of a sick person is avoided by all parties involved until the end. For example, in case 1, although the patient and her family knew the extent of her illness, her family's and friends' efforts were to make sure that she continued to hold on to hope. Ethiopians strongly believe in destiny and in God's power to influence events, especially health events. Their persistence in holding on to hope is tied to their religious belief in God's miraculous powers. The Ethiopian Coptic Christian religion, for instance, places tremendous emphasis on Biblical stories of faith and miracles. Moreover, Ethiopian religious institutions play major roles in healing. Healers including priests and physicians are considered mediators of God's will. For an Ethiopian, giving up hope is against religious teachings and amounts to losing faith in God.

Furthermore, communicating openly about patients' terminal illnesses evokes strong emotional reactions in patients and their families. It also makes family members' imminent separation real. People are afraid that the emotional reaction will be difficult to deal with and may even interfere with the care of the dying. Ethiopian culture restrains most emotional outbursts except at the death of loved ones when great demonstrations of feeling are encouraged. Women tear their clothes and beat their chests to the point that they become sick with grief. Men are excused to cry out loud and shed tears. The loud crying of mourners continues for days after a funeral, revived periodically by the arrival of a close friend or relative who has just found out about the death. Crying at mourning in Ethiopia is collective. Members of a family have to help a newcomer express grief. Professional mourners are hired to stage the collective grieving. Although in the United States they do not hire professional mourners, Ethiopians' traditional grieving practices persist. There have been a few cases where the police were called by their American neighbors because the Ethiopians were disturbing the peace. On one occasion the mourners themselves were threatened with commitment to a mental hospital by the police unless they controlled themselves. In Ethiopian culture, death is the only time persons get to be honest with their feelings and have the uncontested right to express their pain to the whole world. Ethiopians are amazed by the Anglo-Saxon and Northern Europeans' stoic and restrained reactions to death.

Denying the knowledge of an imminent death is mutually understood by the patient and the family. Each is concerned for the well-being of the other and for easing the other's suffering. Even at the last moment of struggle, patients control their emotions to prevent their family from collapsing. The family struggles to do the same so that the patient will not be disturbed by the outburst of emotional reaction to the reality of death until it actually occurs. Indeed, family members are not allowed to cry in front of a dying person to prevent this potentially strong emotion from erupting. Suppressing the knowledge of the imminent death of a loved one is one way of delaying the emotional eruption until death occurs and of enabling the family to continue giving care to the dying patient.

Guidelines for Health Care Professionals

Although most physicians and nurses are overworked and have little time to pay attention and make adjustments to ethnic differences, a little effort in understanding these patients' needs will be gratifying. The following suggestions may help minimize some cross-cultural conflicts, at least for Ethiopian patients.

- Family is important for Ethiopians, and members work as a unit. Therefore, the family should be allowed to participate in a patient's care. Family members will rarely disagree with treatment procedures if they have placed their trust in the physician. While establishing the physician-patient relationship and before communicating a serious medical situation, ask the patient if a family member or a close friend can be designated as a spokesperson. Health professionals should be selective in imparting information to a member of the family; for example, avoid telling the mother or the wife because women are socialized to be fragile. In the absence of an immediate family member, ask for a close friend. Friendship ties are strong among Ethiopians and are even stronger when they are away from their homeland. Friends substitute for the extended family.
- Ethiopians often assess physicians more by the warmth of their manners than by a professional look. A few opening words and show of concern and interest in the patient's background will make a patient feel welcome. If the physician knows something, however trivial, about the refugee's country of origin or culture, mentioning it will break the ice.
- Many Ethiopians appear to be "Americanized," but usually this is superficial. The Ethiopian community is tightly knit, with people socializing mostly with each other, so their cultural values are continually being reinforced. Even those who have been in the United States for a long time and are fully acculturated professionals revert to their cultural roots in times of crisis. This was partly the source of the conflict in cases 1 and 2.

• Ethiopians gravitate to their physicians and their family for reassurance that they will make it through a crisis. Citing statistics or any evidence of a poor prognosis undercuts hope and the will to fight a disease. Partial disclosure seems to work better with these patients. Indeed, some physicians consider full disclosure to be neither possible nor therapeutic. They argue that controlling information is essential to sustain or instill an optimistic attitude in patients, especially those with a poor prognosis.[10] Patients should be reassured that they will make it through. Gloomy statistics can kill, whereas a positive attitude can heal.[23]

• Most Ethiopians have no knowledge of treatment procedures and are willing to let their physicians decide for them. Signing consent forms written for a middle-class American patient is not useful for a refugee who has no knowledge of medical procedures. It may actually induce anxiety. An Ethiopian physician commented that a frustrating experience in his training in American medical practice is in the use of informed consent. He thinks that American medical practice emphasizes the adverse possibilities, which only makes patients anxious. For example, a patient scheduled for an operation is awakened at 6 AM to sign a paper informing the patient of all the odds of not making it through the operation or other untoward events by listing the chances of dying of bleeding, anesthesia risks, and the like. Even though the chances of an adverse outcome are statistically low, what stays with the patient is the dismal information. In Ethiopia, consent for surgical treatment is signed by family members. Physicians here should consider having a designated family member sign such papers to help alleviate anxiety in the patient.

• Ethiopians' pattern of somatization of anxiety and depression and their negative attitudes toward psychiatry are similar to those of other immigrants from the Middle East.[24] Ethiopians resist seeking help from mental health counselors because of the stigma associated with mental illness in their culture. They do not reveal personal information easily and less so at the first clinical encounter. They are socialized to assume that it is improper to reveal oneself fully or to disclose personal secrets to anyone but a close friend. Privacy is further protected by the shared belief that others normally do not have a just claim to information about personal matters.[20] An Ethiopian interpreter said that it is difficult to explain to Ethiopians the need to reveal feelings to a physician. She said that a common Ethiopian phrase is "Just give me the medication and let me go. Why should I tell my life history to a stranger?" Reassuring the confidentiality of requested information is vital.

• Finally, the use of an interpreter is immensely important, not just to translate the medical history and procedures but to assist health care professionals to treat patients in culturally appropriate ways. Except among large groups, most interpreters from the same culture live in the same community, know the patient's family or friends, and cannot be neutral.[25] Much of the time they get caught in a conflicting situation, as in case 3 where there was an emotional conflict between the patient and the interpreter on one hand and on the other hand a cultural conflict between the interpreter and the physician caused by the physician's persistence in relating such distressing information on the spot. This situation could have been avoided by consulting with the interpreter ahead of time.

Judgments about what a dying patient should be told are embedded in cultural, social, and psychological patterns. The anticipated loss of a family member is a painful process that challenges the strengths and defenses of any family. Disclosure of a life-threatening illness is extremely difficult even in American culture.[10] It gets more complicated when the patient is a refugee who is simultaneously undergoing the stress of adapting to a new culture.[11] The physicians who are most successful in gaining the cooperation of refugee or immigrant patients are culturally sensitive to the patients' beliefs and practices.[26] Sensitivity to a refugee's worldview may reduce the frustration and conflict experienced by both refugees and American physicians.

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Cross-cultural Medicine
A Decade Later

- Between 1980 and 1990, Russian immigrants to the US increased by 10,000%, to a total population of around 180,000
- Unlike other immigrant populations, a notable proportion (at least 10%) of Russian emigrés are aged 65 years or older

Older Russian Emigrés and Medical Care

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Although emigration from the former Soviet Union is dramatically increasing nationwide, little information has been reported on the medical problems of these emigrés. For older emigrés in particular, the medical realities of aging, in combination with cultural expectations, make the United States' medical system an arena where the stresses of emigration are expressed and help is sought. We describe the influences of culture and aging on older emigrés' health and interaction with the American medical system. A qualitative, exploratory study was done of problems and issues in health care use by older Russian emigrés at the ambulatory medical clinic of Mount Zion Medical Center, San Francisco. Cultural expectations and beliefs about health, adaptive health behaviors learned in the former Soviet Union, the stresses of emigration, and the medical realities of aging can result in serious problems in the care and treatment of older Russian emigrés. Recommended solutions include educating emigrés and health care professionals, integrating mental health services into the primary care setting, and expanding supportive services in the community such as adult day health care.

(Brod M, Heurtin-Roberts S: Older Russian emigrés and medical care, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:333-336)

Emigration from the former Soviet Union is increasing dramatically nationwide. From 1971 to 1991, about 181,000 Russian Jews entered the United States,[1] and the number is expected to continue to grow.[2] In 1991 alone, 35,219 Russian Jews emigrated, representing two thirds of all Russian emigrés for the year. The greatest proportion come from the former republics of Russia and the Ukraine and have relocated predominantly to major urban areas, including New York, Chicago, Los Angeles, and San Francisco, although most cities have received at least a few immigrants.[1] Secondary immigration patterns make it difficult to estimate accurately the number of emigrés in any given location. About 20% of these emigrés are older than 65 years,[3] making this group one of the oldest immigrant populations.

Little information has been reported on the medical problems of these emigrés.[4] With few exceptions, the implications of immigration for illness behavior and medical care in this population have been either ignored or referred to only tangentially. Yet, for older immigrants in particular, the medical realities of aging, in combination with cultural expectations, make the medical system a natural arena where the stresses of emigration are expressed and help is sought. The medical system often represents a primary area of interaction with American life for this large subgroup of Russian emigrés. The clinic is viewed as much as a place to socialize as to obtain health care.[4]

Unique cultural and aging influences have direct implications for how well this interaction works. Physicians and other health care professionals are at a disadvantage in treating this population because of the lack of information about sociocultural influences on health behavior. In this article we describe these influences and discuss the implications for older emigrés' health and interactions with the medical system. Case examples are presented from an exploratory study conducted with a small sample of nursing staff (n = 2), older Russian patients (n = 8), interpreters (n = 3), and physicians (n = 3) at the ambulatory medical clinic of Mount Zion Medical Center, San Francisco, California. Patients were aged 60 or older, had been in the United States for a year or less, and were all Jews from the former Ukrainian Republic. All of the patients and interpreters identified themselves as "Russians" rather than "Soviets." The interviews were open-ended, semistructured, and standardized. Interviews with Russian patients were conducted with the help of a native Russian-speaking interpreter.

Cultural Expectations and Aging Influences

Reluctant Emigré Status

The emigration policy of the former Soviet Union considered the unit of emigration to be the intact family rather than the individual.[6] When younger members of a family wished to leave the Soviet Union, their aging parents were forced to leave with them if no other younger family members remained behind. As a result, older emigrés have often left their homeland more "for the sake of the children" than because of a personal commitment or desire to emigrate. As one interpreter put it, "You can't leave your old mother or father behind. They must come if they want to or not." It is no wonder, then, that the older Russians were characterized by a medical resident as "genuinely sick, unhappy, displaced people."

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Cohort Effects

This group of older Jewish Russian emigrés, by virtue of their life experiences, is at great risk for having depleted emotional, physical, and financial resources. Many have experienced two world wars, civil wars and political revolutions, religious persecution, Communist rule, inadequate medical care, nutritional deprivation, and economic instability.[4] As Jews, they have spent their entire lives on the edge of society, in constant fear and anxiety about their well-being. For some, the basic reason for migration was rooted in anti-Semitism.[4] "There was insufficient medical care plus there was much suffering in our country," an interpreter explained. "There was the first war, then big starvation, World War II, then Stalin. You cannot live like that and be perfectly healthy."

An older emigré couple described their experience. The wife explained first:

> The cause [of illness] is nervous. He [her husband] frequently visited the psychiatrist. He got depressed. . . . The cause of our illness is immigration and war. After the war I got sick, very sick. I was starving. There was nothing to eat, I was very small and got ill in the stomach.

The husband then related:

> I have the same problems as my wife . . . nervous and depression, no-sleeping attacks [insomnia] at night. The causes are immigration problems in the Soviet Union. We asked to leave, but they refused. We had to wait. I have a high level of sugar, but no care. We had bad conditions of living. We were upset that we were not able to leave.

The wife added: "We lost all our rights. We must stay at home, they took away everything. The cause of illness is that we suffered too much."

Cultural Disequilibrium

Individual Versus Government Responsibilities

In the former Soviet Union the perception of personal responsibility for providing basic necessities differed from that found in the United States. Although conditions may have been harsh and the standard of living low in the Soviet Union, basic survival did not depend on individual work and initiative to the extent that it now does for these people in the United States. All were guaranteed a minimum personal income. An interpreter commented: "They had benefits in Russia, social security, and they think they will have the same here." Soviet emigrés now find themselves in a political and social system where personal initiative and responsibility are stressed. Few emigrés are prepared for the economic and psychological burdens this imposes. For the first time in their lives, they must depend economically and emotionally on either themselves or other family members rather than on the government. A patient said: "Now we are here, there is no problem with food, but other problems. We do not know the language, we are deaf and dumb. We are like children." Another patient said, "In Russia, we all thought we would get jobs, plenty of jobs, we would make money like Americans. Here one month, two months, . . . a year, a year and a half go past, and still no job." Emigrés are simply not prepared for the dire economic straits and dependent status in which some, especially older persons, find themselves; nor are they prepared for the implications of poverty in America.

In addition, many of today's older Russian emigrés were professionals in their homeland. In the United States they are unable to obtain jobs in their fields or are of retirement age. As a result, they are not able to contribute to the family income as they were accustomed to do back home.

Russian Medical System

Medical care in Russia, as well as being state run, adhered to an authoritarian and paternalistic philosophy of care, leaving little room for a free exchange of information.[6] A patient noted: "In Russia, the doctor gives you medicine and you take it. No questions." Also, preventive medicine is virtually unknown. "In Russia, you don't pay attention, you don't think about your health until after you are ill [interpreter]." "In Russia, you only take medicine when you are very sick. Here they push me to take it for prevention. I agree, it's just that I'm not used to it [patient]." In addition, many emigrés have a negative attitude toward the use of mental health services because a psychiatric diagnosis in Russia carried with it severe economic and social consequences ranging from loss of social status to imprisonment.[7]

Expectations of Health Care

Physicians, nurses, and interpreters agree that emigré expectations regarding the American medical system are unrealistically high. "They come expecting as soon as they cross the border 'the doctors will make me well immediately.' There is a big legend [in Russia] about how American medicine is wonderful, so people expect miracles [interpreter]." "They think, 'Here I am in America, America's very great, a very rich country' . . . they want studies, they want a big workup [physician]." An older emigré said, "You [should] go to a doctor if you feel unhappy. In such a country as USA, they will help everyone to be happy and healthy."

Health Beliefs

The interviews suggest that Russian emigrés' perceptions of the causes of illness emphasize the social aspects of health and illness, in contrast to the American biomedical model. In none of the patient or interpreter interviews did respondents mention biologic causes of illness (except starvation) in response to the question, "What causes illness?" Rather, they cited macrosocial factors such as war, immigration, political difficulties, and a poor medical system. The emigrés' explanations of the causes of illness reflected their experience: "I don't know why people get sick here, they should not get sick, because life is not bad here. In the Soviet Union, it is food shortages and housing." The lack of recognition of biologic influences on health or functional status does not reflect naiveté concerning the causes of illness; rather, it demonstrates the Russian health care system's primary emphasis on social and environmental influences on health.

In keeping with this emphasis on social causes of illness was the Russians' characterization of good care. Emigrés were impressed with American medical technology, but the social and personal aspects of health care were considered fundamentally important. Patients expressed appreciation of American physicians' efforts to communicate and explain.

> The doctor has time to take care of patients, they call you and remind you to go. Here the doctors give more attention to the patient . . . it is all about attention here in America. . . . I do like how the doctors explain the problem and find just the right medicine.

Another patient described her and her husband's experience of "good care" in America.

> When in hospital they care for me . . . they helped even without English or Russian, they helped with looks and touch . . . very good attention to him [husband]; they like him and he likes them and everybody is liking all people. They pay attention to him and give him hugs, very good, great.

The psychosocial aspect of health care is of key importance to Russian emigrés.

Realities of Aging

A declining ability to perform activities of daily living, cognitive impairments, sensory deficits, and increased chronic illness combine to make adapting to immigration—learning a new language and a new way of life—all the more difficult and stressful. Older Russian emigrés suffer from the same illnesses that commonly affect aging people—diabetes mellitus, heart disease, and arthritis. Yet many appear to emphasize their symptoms out of proportion to disease activity at any given time.[6] For example, diabetic Russian emigrés report having more impaired function than either Anglo-American or African-American diabetic patients. This impairment is above and beyond the influence of age, disease severity, or duration of illness. Russians with diabetes report substantially greater difficulties coping, perceive more pain, and report poorer overall health than the other two groups.[8] As one physician said, "They seem to have general feelings of . . . unwellness, there are a lot of somatic complaints. They seem to have a great need to be sick." Another physician echoed these thoughts:

> Their complaints are hard to evaluate. They exaggerate comfort complaints, the small things. Chronic complaints of life are blown out of proportion, but the more life-threatening things are put off and not addressed.

Effects of Cultural and Aging Influences

These cultural and aging influences have a profound effect on the illness behavior, medical status, and health care of older Russian emigrés. Cohort effects—particularly a lifetime of inadequate medical care and poor nutrition, in combination with the continued stress of cultural disequilibrium, economic dependency, and reluctant emigrant status—are manifested by high levels of psychological distress and somatic complaints.[5] Emigrés resist using specialized mental health services, preferring to see primary care physicians for psychosocial support and assistance.[7] Counseling services are not trusted by Russian emigrés, and the concept of "just talking" is not culturally valued.[9] In addition, contact with a physician as a high-status person helps to satisfy the needs of these people whose own status and social identity have been compromised by emigration. A patient discussed what he did when experiencing emotional difficulties: "You can talk to a relative or a friend, but you can go to a doctor as well. My cardiology doctor is the best psychiatrist, better than going to a psychiatrist. He knows me."

The problem is well recognized by clinic staff. For example, a nurse explained:

> Usually they have simple problems that can be better taken care of by discussion, not medication. They're lonely; they need attention; they need company. There's lots of depression . . . they come here to talk to the doctors, to talk to us. They come here to socialize, that's what they need . . . not medication.

Unfortunately, emigrés' negative attitudes toward mental health services prevent them from seeking appropriate mental health care. Rather, they seek "a cure" from their physician, who is often ill equipped to deal with emotional problems or simply does not have enough time. Real problems of depression and demoralization are not addressed, and the emigrant returns again and again in hopes of feeling better. The result is excessive and inappropriate use of medical services.

Immigrants rely on old habits and operate under expectations that are inappropriate in a new environment. Emigrés do not fit easily into the American medical system and, as misfits, are neither subtle nor quiet. They are accustomed to literally having to make noise to receive care in Russia; they have been described as pushy, manipulative, and abrasive.[6] "They are nice people but 'over-everything,'" said a clinic nurse:

> They overdo, they are overbearing. They had to demand more in Russia to get anything; they had to be pushy. . . . If you ask why they want to be seen, they will say chest pain; they know it is the worst thing they can say. They know that we will have to see them. It has worked before; it will work again.

Older emigrés are accustomed to living in a society of scarcity and so have become proficient in "working the system" to obtain needed services.[9] These behaviors, which worked well in the Russian system, are maladaptive in America but are still used. An interpreter explained:

> They come from a different system full of corruption. You are supposed to have a right to care, but there is much corruption. You have to pay and bribe. They think it is the same here. . . . We come from a rotten system, always standing in line. In Russia, you get out of line and come back because everyone is used to just standing there. They think they can come back here, and it makes people angry.

The medical system is often the Russian emigrés' primary point of interaction with American society. Emigrés recognize early on that the medical system, particularly physicians, acts as a gatekeeper to a broader world of social benefits.

> Here privileges depend on what the doctor says, whether you have a right to SSI, welfare, and so on. They want everything immediately in their first month so they pressure the doctor. They are scared,

observed a Russian interpreter. According to a physician,

> [Russian emigrés] tend to have very high expectations that multiple services can be endlessly provided. They seem to believe there is no end to social, medical, and financial supports. They tend to feel that supportive services are necessarily linked to health care.

A clinic nurse echoed this opinion: "They use the system to get what their needs are: housing, money, whatever, transportation vouchers. They use the medical system to get all their needs met." Another physician reflected on the problem: "Part of it's they're just trying to grab and become part of the system. I'm sure they feel displaced, and they're kind of lost." Again, emigrés' use of the medical system is frequently viewed by health care professionals as excessive and inappropriate.

Misunderstandings on the part of emigrés about how the system works adversely affect continuity of care and further decrease quality of care. Patients consistently complained that they always saw a different physician at the clinic, and each time they had to retell their medical and social history. Physicians, too, complained about a lack of continuity in treating Russian emigrés:

> They should have a primary care doc, but they're only available at certain times . . . they need to understand how to get a primary doc and how to keep them . . . right now they can't make the best use of the system.

The jarring incongruence in expectations creates a tension that is almost palpable in many clinics serving Russian patients. Physicians feel frustrated and often helpless in treating this group, often labeling them difficult or resistant patients. As one physician commented, "I become very frustrated with what they want and what I can actually give them."

Along with being frustrated, physicians are concerned

that the care they are providing is inadequate due to language problems, inadequate information on and preparation for treating the Russians, and the emigrés' inadequate understanding of the American medical system.

> We need education, we weren't really told anything about treating Russians or what happened in Russia . . . now I just sort of limp through day by day. You learn by practice, trial and error . . . often it's like veterinary medicine . . . there's a lot of guessing,

complained a medical resident. Another physician admitted:

> Treating the Russians is scary. You can't know what you need to know in the time given. I worry about missing things . . . I think I'm getting a sense of how to make that leap of judgment, but I'm not very comfortable with it.

Another physician summed up the worries and concerns American physicians have in treating Russian emigrés:

> Their problems are psychosocial. We need some kind of support . . . there's just nothing for them. And we need education as to what is their baseline. . . . What is health care like in Russia? What was their health before? How can you tell what's really a depression in a Russian and what's not? How do you deal with it? What do they want? What are they used to?

A vicious cycle is set into motion between patients who feel the medical system is unresponsive to their needs and physicians who feel they are forced to deal with difficult patients. The physician-patient relationship suffers, and, as a result, the quality of care is diminished.

Ironically, the Russians interviewed felt they were getting good care. They claimed to be thoroughly satisfied with their experiences, and the interviewer had to press them to say anything negative at all about their health care. When pressed, they admitted they did not like the occasional long waits in clinics or business offices and were unhappy that they had to speak to their physicians through interpreters. Otherwise, "they never complain about the doctor or quality of health care, just the mechanics of the system," observed a Russian interpreter. Emigrés spoke in consistently positive terms about the care they had received. "I am satisfied, yes, yes, the doctors are good, the service is good, everything is good." One must wonder whether this emphatic statement of satisfaction with care could be the result of fear and a mistrust of criticizing bureaucracy or of speaking too freely about dissatisfactions.

Health Status Implications

It is widely recognized that cultural health beliefs influence health behavior.[10] The emigrés' social explanations for illness, reduced perceptions of personal responsibility for health care and impaired functional status, and lack of appreciation of preventive health care have adverse implications for their ability to learn self-management. Emigrés often do not understand the rationale for or perceive a need to engage in self-management of their illnesses. Because these behaviors are vital to the control of many chronic illnesses for which older persons are at increased risk, older Russian emigrés are at greater risk for complications from diseases such as diabetes mellitus, cardiovascular disease, and hypertension.

Impaired functional status in older Russian emigrés, particularly increased perception of pain, also has major implications for both the quality and the quantity of patient interactions with the medical system. Pain is one of the most frequent reasons why older persons in general seek medical care. Pain causes health-related problems such as physical limitations,[11-13] mental health problems,[14] social limitations,[11,12] and sleep disorders,[11] all of which may lead to an increased use of health care services and higher costs.[13] One nurse said, "They magnify normal aches and pains but then aren't concerned about what the tests find because that is not what they think is important." To the extent that these problems are related to the pain, the recognition of pain and pain-related problems by health care professionals is essential to adequate care. Greater perceived pain may account for some of the reported overuse of services by older Russian immigrants.[4]

Conclusion

To address the conflict in the interaction between older Russian emigrés and the US medical system, the dynamic relationship between sociocultural and aging influences must be understood and appreciated. Behaviors learned during a lifetime spent in a different cultural and political reality are ingrained. For American health care professionals, these behaviors may be difficult to understand or respect.

The solution begins with education for both emigrés and physicians. The emigrés must be taught how the American system works and its underlying philosophy. Physicians must be educated about the cultural influences that have shaped the behavior and attitudes of the emigrés. Reshaping the system to integrate mental health services into the primary medical care setting would address the Russian reluctance to seek mental health services outside of the medical system. In addition, programs such as adult day health care and senior day care programs can be targeted to older Russian emigrés to provide a setting in which social support, health services, and acculturation can occur. The experience of L'Chaim, the Russian Adult Day Program of the San Francisco Institute on Aging, has been promising in this regard. Decreased levels of depression and somatic complaints and fewer requests for medical care by emigrés have been reported after participation in that program.[15]

The plight of older Russian emigrés is simply expressed by an elderly Russian woman: "In Soviet Union, medicine is different. It is difficult to change."

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Cross-cultural Medicine
A Decade Later

In 1990, a total of 22.3 million people of Hispanic origin lived in the US Various Hispanic populations not only tend to live in different regions of the US but are different in educational, occupational, economic, cultural, and health background

Getting By at Home
Community-Based Long-term Care of Latino Elders

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Although evidence suggests that the morbidity and mortality of Latino elders (of any Hispanic ancestry) are similar to those of non-Latino whites, Latinos have higher rates of disability. Little is known about influences on the use of in-home health services designed to assist disabled Latino elders. We examine the effects of various cultural and structural factors on the use of visiting nurse, home health aide, and homemaker services. Data are from the Commonwealth Fund Commission's 1988 national survey of 2,299 Latinos aged 65 and older. Mexican-American elders are less likely than the average Latino to use in-home health services despite similar levels of need. Structural factors including insurance status are important reasons, but acculturation is not pertinent. Physicians should not assume that Latino families are taking care of their disabled elders simply because of a cultural preference. They should provide information and advice on the use of in-home health services when an older Latino patient is physically disabled.

(Wallace SP, Lew-Ting CY: Getting by at home—Community-based long-term care of Latino elders, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:337-344)

Mrs Martinez is an 81-year-old widow with dementia. Her Alzheimer's disease is now at the point where she has trouble bathing and dressing independently. Although she lives alone, her daughter brings her in for medical visits and acts as a translator. The daughter has mentioned that at least two other family members also visit Mrs Martinez regularly. Born in Mexico, Mrs Martinez is a permanent United States resident with Medicare and Medi-Cal (California's Medicaid program) benefits. Should a physician discuss long-term care options with the family?

Long-term care services exist to compensate for lost (or never existing) functional capacity.[1] Yet few patients or families know about the range and availability of services in their communities.[2] Long-term care is often erroneously equated only with nursing home care. Physicians play a key role because older patients and their families commonly turn to them for information and assistance.[3]

Various factors influence the interest and ability of Latino families (of any Hispanic ancestry) to seek formal long-term care. Most of the influences can be placed into two broad categories: cultural and structural. We focus on identifying patterns of use of community-based in-home long-term care health services by Latino elders. We compare the relative importance of cultural and structural factors associated with the use of those services and relate those findings to clinical practice.

The issue of in-home care takes on increased importance when the future demographics of Latino communities are considered. First, the number of Latinos older than 65 is projected to increase by 500% by the year 2030.[4] This will increase the strain on the family and informal resources that currently provide care. Second, that strain will be compounded by the declining size of families of minority groups, further reducing the availability of informal care to the growing number of aged.

Health Status and Needs of Older Latinos

We typically discuss the health of minority populations in reference to those with the best health status in the United States, usually non-Latino whites. The status for older Latinos is mixed, however. Compared with non-Latino whites, older Latinos have better health indicators in some areas and worse in others.

A common indicator of the health status of populations is death rates. Unfortunately, ethnicity (Latino versus non-Latino) is not reported by all states and is often missing for some states that do report it. From 1979 to 1981, 13 of 15 states* that were home to about 45% of the Latino population provided usable data on Latino deaths. In those states Latinos aged 65 and older had lower death rates than older non-Latino whites for almost all causes, especially diseases of the heart (a third lower), chronic obstructive pulmonary diseases and allied conditions (50% lower), and malignant neoplasms (almost a third lower). Higher death rates occurred among older Latinos for diabetes mellitus (twice the non-Latino white rate); motor vehicle accidents (three-fourths higher);

*Arizona, Colorado, Georgia, Hawaii, Illinois, Indiana, Kansas, Mississippi, Nebraska, New York, North Dakota, Ohio, and Texas reported death rates according to ethnicity. California (which has the largest number of Mexican Americans) and Florida (which has the largest number of Cubans) did not differentiate death rates according to ethnicity.

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ABBREVIATIONS USED IN TEXT

ADL = activities of daily living
IADL = instrumental activities of daily living

nephritis, nephrotic syndrome, and nephrosis (two-thirds higher); and chronic liver disease and cirrhosis (two-thirds higher). The pattern for older Mexican Americans and Puerto Ricans was similar, except that death rates for chronic liver disease and cirrhosis were higher for Puerto Ricans and the death rates for diabetes mellitus were between those of Mexican Americans and non-Latino whites. The death rates of older Latinos average a fifth lower than those of non-Latino whites, with the Latino mortality advantage greatest among older men.[5] More complete data for 1987—18 states including California—show similar results, with heart disease accounting for an even lower proportion of the total number of deaths of older Latinos and malignant neoplasms accounting for a somewhat higher proportion.[6]

Morbidity patterns provide a similar variation in incidence of diseases. For most major diseases except diabetes, Latinos appear to have lower rates of illness than non-Latino whites. Both age-adjusted and age-specific hypertension rates are substantially lower for Latinos than for non-Latino whites,[7] contributing to a lower Latino prevalence of coronary heart disease and stroke.[8] The overall age-adjusted incidence of cancer in Latinos is also lower than that in non-Latino whites (246 versus 335 cases per 100,000 population). Latinos have a lower incidence of cancer of the breast, lung, and colon-rectum. The rate is about the same for prostate cancer, and Latinos have a higher rate of stomach cancer.[8] The most notable disease for which Latinos clearly have a higher prevalence is diabetes. Self-reported diabetes is two to three times more common among Mexican Americans than among all whites. The prevalence of diabetes increases with age, with 22.7% of Mexican Americans aged 65 to 74 reporting diabetes[9] versus 9.3% of all whites aged 65 and older.[10]

Although the death and disease patterns for older Latinos show several advantages over older whites, disability and other health indicators are worse for older Latinos. Older Latinos averaged eight more days of restricted activity from 1978 to 1980 than non-Latino whites but ten fewer days than non-Latino blacks (Table 1). Puerto Rican elders reported more restricted activity days than any group. Health status declines with income, but even when we look only at low-income elders, the pattern persists. A more severe measure of disability is the number of days that an older person is confined to bed during a year. That measure shows that both older Puerto Ricans and Mexican Americans were more disabled than non-Latino African-American or white elders. The rate of activity limitation due to chronic conditions for older Latinos was between that of older non-Latino African Americans and whites. The most commonly used indicator of general health status is self-assessed health. Table 1 shows that more than a third of older Latinos reported their health as fair or poor (versus good or excellent). This is slightly higher than the proportion of older non-Latino whites but substantially lower than the proportion of older non-Latino African Americans.

Our overall knowledge of the health status of Latino elders is complicated by data inadequacies. In general older Latinos have better health than non-Latino whites in death rates and prevalences of certain life-threatening chronic diseases. The major disadvantages for older Latinos include their higher prevalence of diabetes, their greater activity limitations, and their lower global (self-assessed) health status. Because older Latinos are disadvantaged in activity limitations, examining factors that influence the use of community-based long-term care is important.

Use of Health Care Services by Latino Elders

Although health status data indicate the potential importance of community-based in-home health services, most of the research on health care use by Latino elders has focused on the use of physicians and hospitals. In both areas older Latinos appear to receive similar or more care than older non-Latinos. Older Latinos have more physician visits per year than either non-Latino whites or African Americans (Table 2). This pattern holds even for those reporting poor or fair health. Less variation occurs in the rates of hospital admissions, although older Latinos are slightly more likely to use a hospital than older non-Latino whites or African Americans.

A different pattern emerges when we control for factors that influence physician and hospital use among middle-aged and older Latinos. Puerto Ricans and Mexican Americans are more likely than non-Latino whites or African Americans to see a physician as their physical activity becomes limited, even after controlling for age, sex, health status, and other factors. On the other hand Puerto Ricans and Mexican Americans are less likely to be admitted to hospital when they rate their health as poor.[13]

Limited data exist on the use of long-term care services by Latino elders. Most data show that older Latinos are less likely than either older whites or African Americans to use

TABLE 1.—*Health Status of Latinos, Non-Latino Whites and Non-Latino African Americans Aged 65 and Older*

Health Status	*All Latinos*	*Mexican Americans*	*Puerto Ricans*	*Non-Latino Whites*	*Non-Latino African Americans*
Restricted activity, days/person/yr*	46.5	52.8	61.4	38.7	56.9
Restricted activity in families with income < $10,000/yr, days/person/yr*	55.0	58.8	84.0	45.4	62.5
Bed disability, days/person/yr*	20.7	26.1	35.7	12.9	22.9
Activity limitation due to chronic condition, % of persons*	47.5	52.4	52.6	44.3	57.2
Fair or poor self-assessed health, % of persons†	35.2	32.0	37.5	29.0	46.8

*Data are from 1978 to 1980.[11]
†Data are from 1987.[12]

TABLE 2.—*Use of Health Services by Latinos, Non-Latino Whites, and Non-Latino African Americans Aged 65 and Older**

Health Service	All Latinos	Mexican Americans	Non-Latino Whites	Non-Latino African Americans
No. of physician visits/person/yr	8.2	9.1	6.3	6.7
No. of physician visits for those with fair or poor self-assessed health/person/yr	11.5	12.1	9.6	8.9
≥1 Hospital episodes, % of persons	18.7	18.5	18.3	17.3

*Data are from 1978 to 1980.[11]

nursing homes,[14,15] even after other risk factors are taken into account.[16] The higher level of disability for Latinos in the community may be partly because disabled Latinos remain in the community when similarly disabled whites use nursing homes.

In-home health care is viewed as an alternative to institutionalization, but we know little about the effects of race, ethnicity, culture, and class on the use patterns of community-based and informal long-term care services.[17] Older Latinos and non-Hispanic whites use paid in-home care in about the same proportions nationally, whereas older Latinos receive more informal care.[18] This does not, however, control for level of disability, availability of family, financial status, or other factors that might increase or decrease the need for formal and informal care.

A study of case-management clients in Arizona found that older Latinos were less likely to use community-based long-term care services than non-Latino whites despite their greater activity limitations.[19] The lower level of formal support received by Latino elders was balanced, however, by higher levels of informal support. Greene and Monahan caution that their data do not indicate whether the family support was provided because formal support was not available or in preference to formal services. This distinction between service use patterns as a result of preferences versus barriers in the structure of the health care system forms the core of the debate over differences in the use of health services by minority elders.

Culture and Institutional Structure Influencing Health Care Use

Forces that influence the use of health services by minority elders can be divided into two general categories: cultural and structural. Cultural influences include the belief systems, behaviors, and preferences of a group that might cause certain patterns of health care use. Structural influences include the way the health care system and other social institutions are organized and operated. They may present both incentives and barriers to the use of health services.

Culture. Cultural influences would be expected to shape the use patterns of long-term care, especially because long-term care often involves nontechnical assistance that can be provided by family members. Culture may influence the use of family versus paid care through concepts of family responsibility and attitudes toward the use of public services for those eligible for Medicaid. The strength and centrality of family are common Latino values.[15] A possible explanation of why Latino elders use nursing homes less often than do non-Latinos is that Latino family roles make Latinos more disposed than non-Latinos to make the sacrifices necessary to help older relatives.[20]

Culture can also influence how satisfied patients are with their medical care. Health care professionals' lack of knowledge about Latino cultural norms and inability to communicate in Spanish are often cited as factors discouraging Latinos from seeking needed health care.[21-23] Acculturation—an immigrant's adoption of attitudes and common behaviors from the dominant society—can affect both family functioning[24] and health service use.[25] It is surprising, therefore, that most research on health care for Latino elders has not expressly investigated the importance of acculturation (others[26] also note this deficiency). Although acculturation does not necessarily weaken Latino family functioning overall,[27] there is evidence that acculturated families provide lower levels of informal support to the aged.[28] Thus, we might expect acculturated Latino elders to use more formal services than traditional Latino elders.

Institutional structure. Income and health insurance are the most important structural determinants of a person's ability to obtain health care. Older Latinos are disproportionately poor because of the structure of our occupational and economic system. Also, our health care system rations care based on ability to pay. Almost all older people have insurance coverage for acute care from Medicare, but Medicare pays less than 6% of all long-term care costs in the United States.[29]

Given the importance of income and insurance in determining long-term care use, there is a major gap in the health insurance status of Latino elders. In the general population many more Latinos are uninsured (33%) than whites (13%) or African Americans (19%). This is largely because Latinos are concentrated in industries such as personal services and construction that do not offer insurance and because they disproportionately live in states—Texas and Florida—with stringent Medicaid eligibility criteria.[30] As a result, serious illness in the family is considered a financial problem almost twice as often among Latinos as other whites (39% versus 19%).[31]

Retrospective Study

The following analysis reports on the use of in-home health services for all older Latinos and for specific Latino subgroups. Their use of services is examined by need, individual characteristics, family status, acculturation, and health insurance.

Methods of Analysis

The data were from the 1988 national survey of Hispanics aged 65 and older sponsored by the Commonwealth Fund Commission on Older People Living Alone. Telephone interviews, done primarily in Spanish, were conducted of 937 Mexican Americans, 714 Cuban Americans, 368 mainland

Puerto Ricans, and 280 other Hispanics.* The data were weighted to reflect US population estimates. The survey contractor's final report contains a complete methodologic discussion.[32]

We were primarily interested in explaining the previous year's use of in-home health services (home health nurse, home health aide, or homemaker). We focused on these services for two reasons. First, these services are often covered by Medicaid, Medicare, or both, and target the most disabled elders. Second, physicians are central to these services because physician certification of need or a care plan is required before Medicare or Medicaid will pay for them in many situations. Even when physician approval is not necessary, physicians can be an important source of referrals.

Explanatory variables include five health status indicators as evidence of need for in-home services: limitations in activities of daily living (ADL)—bathing or showering, dressing, transferring, walking, getting outside, using the toilet; limitations in instrumental activities of daily living (IADL)—preparing own meals, managing money, using the telephone, doing light housework, doing heavy housework; self-assessed health status; hospital admission within the past year; and frequent physician visits in the past year.

Demographic and social characteristics are often associated with differences in the use of health services. We examined the demographic variables of sex and age. Social level variables are subject to intervention and change. They include indicators of traditional culture (acculturation), education, social support (living alone, living with spouse, living without spouse but with or near children), income (poverty), and health insurance.

Two variables are frequently used to indicate levels of acculturation: language ability[21,33] and age when the respondent arrived on the US mainland.[34] We created a summary variable that includes both of these dimensions and can be interpreted as the extent of acculturation of the respondent in comparison to the average level of acculturation (low) of all older Latinos.

Results

Needs and resources of Latino elders. The need for in-home health services for older Latinos appears to be substan-

*The largest nationality was Dominican (95 interviewees) followed by in decreasing frequency Spanish, Colombian, Salvadoran, Ecuadoran, Nicaraguan, and 15 other nationalities.

TABLE 3.—*Characteristics of Latinos Aged 65 and Older by Subgroup**

Characteristic	*All Latino Elders,†* %	*Mexican American,* %	*Cuban,* %	*Puerto Rican,* %	χ^2 *Statistical Significance‡*
Health					
1 or more ADL difficulty	39.1	39.6	32.0	44.6	.005
1 or more IADL difficulty	53.4	54.5	44.8	54.3	.005
Self-assessed health—fair or poor	53.3	57.0	46.7	62.7	.000
Hospital use past year	22.1	20.7	21.5	31.8	.001
Physician use ≥ 12 times past year	23.9	20.5	28.8	36.7	.000
Demographic					
Women	55.9	53.2	61.7	55.8	.019
Aged 65-74 yr	62.1	62.3	54.7	69.5	.001
Social					
Immigrated at age 55 or older	16.0	6.2	41.4	13.1	.000
Immigrated at age 31-54	21.2	10.6	49.8	40.4	
Immigrated at age 17-30	12.1	12.4	5.3	34.2	
Immigrated at age 0-16	12.4	17.9	3.0	12.3	
Born in US/mainland	38.4	52.9	0.5	0.0	
No English (monolingual Spanish)	39.4	33.8	57.3	37.4	.000
Poor English§	32.5	37.4	30.6	37.3	
Speaks English well	28.1	28.7	12.1	25.3	
<5 yr school	42.5	54.3	17.1	41.5	.000
6-11 yr school	38.7	33.8	49.1	45.1	
High school graduate and up	18.7	12.0	33.8	13.4	
Lives alone	22.4	22.3	23.1	26.2	>.05
Lives with spouse	48.7	50.0	44.6	46.5	>.05
Without spouse, lives with children or within 30 min	36.6	38.1	33.5	35.6	>.05
Family income					
Above poverty	31.9	29.8	37.6	30.5	.005
Below poverty	42.2	45.1	35.8	41.8	
Unknown or refused	25.9	25.1	26.6	27.7	
Covered by Medicare	79.9	79.6	87.3	79.8	.007
Covered by Medicaid	42.2	39.0	52.8	50.7	.000

ADL = activities of daily living, IADL = instrumental activities of daily living

*Weighted to reflect United States population estimates for older Latinos
†Includes "other Hispanics," not presented separately
‡Significance of χ^2 comparisons among three subgroups is given.
§Primary language is Spanish and reports fair or poor English ability

tial but varies among the groups. In general older Puerto Ricans have the highest levels of need, followed by Mexican Americans and Cubans. More than a third of all older Latinos had one or more difficulties in ADLs, more than half had one or more difficulties in IADLs, and more than half reported fair or poor health (Table 3). More than two fifths of all older Latinos had a hospital admission, and more than two fifths saw a physician at least 12 times during the past year. Older Puerto Ricans had the highest use of medical services. The high ADL and IADL dependencies, the low self-assessment of health, and the common use of physician and hospital care reinforce the data presented earlier showing a high need by Latino elders for community-based long-term care.

The older Latino population includes more women than men, with most elders in the "young elderly" range (ages 65 to 74). The Cuban population had even more women and were older, reflecting their different history of migration to the United States.[35]

Some social characteristics (Table 3) are liabilities for those needing supportive services, including recent immigration, limited English, low education, and poverty. Only half of the Mexican-American elders and almost no Cuban or Puerto Rican elders reported being born in the United States. A sizable proportion, especially Cubans, immigrated at age 55 and older. Almost 40% of older Latinos reported speaking no English, even though more than a quarter reported good English skills. Almost half of the older Latinos had less than a primary school education. A third of older Cubans, however, were high school graduates. Poverty is a common problem that is most acute among Mexican-American elders.

Resources for disabled Latino elders potentially include health insurance and the availability of family. Most older Latinos live with a spouse or without a spouse but with or near (within 30 minutes of) their children. The living arrangement is the only characteristic where there are no statistically significant differences between the Latino subgroups. Although most older Latinos have Medicare, the proportion without coverage is twice the national average.[32] On the other hand older Latinos have high rates of Medicaid coverage, partly as a result of their high poverty rates. Mexican-American elders, however, have the highest poverty rate and the lowest Medicaid rate.

Characteristics of each group reflect its immigration and occupational history. Older Mexican Americans are most likely to have been born in the United States but have had limited occupational opportunities and have faced housing discrimination.[35] Among this group, for example, 21% reported farm work as their primary lifetime occupation.[32] This history explains why older Mexican Americans have the lowest educational levels, only average English abilities, above-average poverty rates, and incomplete Medicare coverage (Table 3). In addition, some older Mexican Americans avoid government programs, such as Medicaid, and services because they are undocumented residents. In the 1986 immigration legalization program, 1% of Mexican immigrants applying to regularize their status were aged 65 or older.[36] In contrast, older Cubans include many professionals who immigrated as adults after the end of the Cuban revolution in 1959.[37] Consequently, Cuban elders have the most education, the least English ability, and oldest ages at the time of immigration. They can receive Medicaid because of their special refugee status.[38] Puerto Ricans are like Mexican Americans in most social characteristics, although no Puerto Rican elder in this survey was born on the mainland. Puerto Ricans, however, are all US citizens as a function of the commonwealth status of Puerto Rico and therefore never face immigration status barriers to the receipt of Medicaid.

Use of services. Given the high levels of disability among the Latino elders, we expected to find high levels of service use. Table 4 shows the high use of community services, with some differences by subgroup. Visiting nurses were the most commonly used in-home health service, followed by homemakers and then home health aides. The higher use of most in-home health services by older Puerto Ricans mirrors their higher levels of disability and poorer health. Mexican-American elders use in-home health services less than Cuban elders in two of the three services, but this lower use does not reflect any health status differences. It is important to note that each population is concentrated in different areas: Puerto Ricans in New York City, Cubans in Florida, and Mexican Americans in the Southwest. Some of the differences in use may have resulted from differences in the availability of services in the different areas.

TABLE 4.—*Use of 3 Different In-home Health Services in Previous Year in Older Latinos by Subgraup, 1988**

Health Service	*All Latino Elders,†* %	*Mexican American,* %	*Cuban,* %	*Puerto Rican,* %
Visiting nurse‡	9.3	8.6	9.9	15.9
Health aide§	5.1	4.1	6.7	7.0
Homemaker‖	7.2	6.0	9.0	14.2
Any in-home health service§	14.8	13.2	18.4	22.0

*Sample data were weighted to reflect United States population estimates for older Latinos.

†Includes "other Latinos" not presented separately

‡Puerto Ricans differed from other 2 groups at $P<.05$; no statistically significant difference was seen between Mexican Americans and Cubans.

§Mexican Americans differed from other 2 groups at $P<.05$; no statistically significant difference was seen between Cubans and Puerto Ricans.

‖All between-group differences were significant at $P<.05$.

Correlations show the relationships between the use of in-home health services and the needs, individual characteristics, and social characteristics of each subgroup of Latino elders (Table 5). For correlations that are statistically significant, we need to compare the size of the correlations to determine the practical relevance. In particular, the correlations show the relatively high importance of need factors and Medicaid and the relatively low importance of cultural factors.

The need indicators of ADL and IADL disability have the largest correlations with the use of in-home health care (Table 5). Medical care use—hospital and frequent physician care—has smaller but important correlations with the use of in-home health care. The only other correlations similar in magnitude to the need indicators are advanced age and receipt of Medicaid. Smaller correlations include the negative relationship—decreases the chance of service receipt—between living with a spouse and in-home health services. For Mexican-American and Puerto Rican elders, living alone increases the chance that services will be used.

As we would expect, ADLs, IADLs, and being admitted to a hospital are each predictors of in-home health service use. Part of the role of visiting nurses, homemakers, and home health aides is to assist the disabled elderly with ADLs and IADLs or other needs those impairments might create.

Similarly, the push to discharge the elders from hospitals as early as possible has moved some of the care formerly provided in the hospital into the home, increasing the need for posthospital nursing and other care.[39] Further analysis, not presented here, found that self-assessed health and physician visits did not predict the use of in-home health services after controlling for other variables.[40] Both a global assessment of health as poor and frequent physician visits can be the result of a variety of health conditions not related to a disability that requires long-term care. Consequently, older Latinos who use in-home care are more likely than non-in-home care users to see a physician (the correlation), but physician use itself does not increase the use of in-home health services.

Mexican-American and Cuban men are somewhat less likely to use in-home health services than women (Table 5) because they are generally younger than the women and more likely to be living with a spouse. Gender by itself does not influence the use of in-home health services.[40] Frail older Latinos (age 75 and older) are more likely to use in-home services independent of need and social factors.[40] Age may increase the number and severity of disabilities (we only measured their presence) or weaken informal support (for instance, an aging spouse may no longer be physically able to provide the same level of assistance), or both.

TABLE 5.—*Correlations of Use of In-home Health Services by Older Latinos by Subgroup, 1988**†

Characteristic	*All Latinos*	*Mexican Americans*	*Cubans*	*Puerto Ricans*
Need indicators				
ADL (1 or more)	.30	.29	.28	.36
IADL (1 or more)	.27	.25	.33	.33
Self-assessed health—1 = fair or poor, 0 = excellent or good	.17	.18	.18	.12
Hospital admission past year—0 = no, 1 = yes	.28	.25	.26	.23
Frequent physician use 1 = ≥12/yr	.13	.11	.11	.23
Individual characteristic				
Sex—0 = female, 1 = male	–.08	–.11	–.12	–.09†
Age, yr—0 = 65-74, 1 = ≥75	.23	.24	.24	.24
Social characteristic				
Acculturation	–.04	–.01†	–.05†	–.10†
Education—<6 yr, 6-11 yr, 12 yr and up	–.05	–.03†	–.06†	–.18
Live alone—0 = no, 1 = yes	.12	.17	.02†	.15
Live with spouse—0 = no, 1 = yes	–.11	–.09	–.13	–.15
Live without spouse and with or near children—0 = no, 1 = yes	.02†	.01†	.02†	.02†
Family poverty—0 = no, 1 = yes	.09	.10	.01†	.19
Medicare—0 = no, 1 = yes	.09	.07†	.00†	.16
Medicaid—0 = no, 1 = yes	.20	.17	.19	.17

ADL = activities of daily living, IADL = instrumental activities of daily living

*Sample data are weighted with the normalized weights.

†All correlations are significant at $P<.05$, except those with †'s, which are not statistically significant.

As we expected, we also found correlations between in-home health care use and some of the social resources. Living alone, which indicates a lower level of available support, increases the chance of using in-home health services for most subgroups. Accessibility to family help, as indicated by living with a spouse, reduces the use of in-home services. When other variables are controlled, living without a spouse but with or near children also reduces the use of in-home health services.[40] What the data do not show is the causal order—whether family is used in preference to formal services or because formal services are unknown or unavailable. Latino elders with Medicaid coverage are more likely to use services,* demonstrating the importance of financial barriers to in-home service use. Medicaid can pay for in-home health services, reducing the financial burden for low-income Latino elders.

The small and not statistically significant correlations with some variables are as important as the larger correlations just described. In particular, acculturation has an unexpectedly small or not significant correlation with the use of in-home health services (Table 5). Similarly, despite the emphasis on family in Latino culture, the accessibility of children for those living without a spouse had no statistically significant correlation with the use of in-home health services. Acculturation, which was measured by knowledge of English and age at immigration, had no relevant correlation with in-home health service use. Even when controlling for other variables, acculturation remained not significant. Similarly, graduation from high school had no independent effect on the use of in-home services.[40] The lack of any overall acculturation effect supports the conclusion that family support is not primarily a result of a strong cultural preference for family help. Cuban elders had few significant correlations of social characteristics with service use.

After controlling for all the other variables, Puerto Rican elders are still twice as likely to use in-home health services as the other Latino groups.[40] This is possibly because older Puerto Ricans commonly live in New York City, which has a relatively well-developed network of in-home services compared with other parts of the country (V. Levy, New York City Department for the Aging, oral communication, November 1991). Similarly, Mexican-American elders may have lower in-home health service use because some live in nonurban areas and in states where fewer services exist.

Summary

Latino elders comprise a diverse set of subgroups.† Our data show that all subgroups frequently have functional limitations and low health status, with Puerto Ricans having the worst health. Acculturation has little or no effect on the use of in-home health services for any subgroup, whereas structural factors such as health insurance and the local availability of services have a moderate effect on all subgroups. These structural factors are the most likely reason that Mexican-American elders use in-home health services less than the other subgroups.

Structure or Culture—What Does It Matter?

In an ideal health care system, the use of services would be determined only by need and personal preferences. Our data show that need factors are among the strongest predictors of the use of in-home health services. We consistently

*The increased chance of use by those in poverty is mostly caused by those in poverty being more likely to have Medicaid, to live alone, and to have ADL or IADL limitations, each of which independently increases the use of in-home health services.

†There were not enough Central Americans in the sample to form any generalizations, but those living in the Southwest probably have many characteristics similar to Mexican-American elders: a significant proportion will be undocumented residents, and most will have low incomes, low Medicaid coverage, and low in-home health service use. Few will have been born in the United States.[41]

found, however, that health insurance status and living arrangements also influence the use of in-home health services. If we are to ensure that Latino elders receive appropriate health services, we need to understand the extent to which structural and cultural forces are also involved in the use of services.

The importance of living arrangements—especially after other factors are taken into account—could be described as the result of a cultural preference for family help in place of formal assistance. Acculturation has no significant effect, however, which contradicts the interpretation that reliance on family in place of formal in-home health services is a simple cultural preference. The more likely explanation is that families could use and benefit from the extra help provided by in-home health care, regardless of their cultural orientation. Latino elders, their families, and all other elders, however, generally have a low awareness of the existence and purpose of in-home health services.[2,3] Their low-income backgrounds make them less likely to think that paid help is feasible.

A moderate use of physician services did not independently increase older Latinos' use of in-home health services, despite the fact that the physicians are the most common source of information about long-term care in the general population.[3] If most physicians assessed the disabilities of the older Latino patients they see often and made referrals to in-home health services when indicated by need, we would expect to see physician visits independently associated with increased service use.

One reason physician visits may not increase in-home health services use is that many physicians may observe the family providing in-home assistance and assume that such assistance is provided for cultural reasons. It is possible, however, that the family assistance is provided because the elder and the family are not aware of the range of options available or are deterred by the complexity of the long-term care system and its financing. Families may also think that because care giving has not yet become a crisis, it is not appropriate to ask for additional help. For Latino elders who have Medicaid and therefore access to a case manager, it would be helpful for physicians to assess the functional disability level of their patients and counsel their disabled older Latino patients about the range of community services available to supplement the care they may already be receiving from their families. Research on the general older population finds that formal services complement rather than replace the efforts of family.[42] Older Latinos often hold expectations of assistance from their families,[21,43] but those expectations do not mean that formal services would not improve the status of the elders and their care givers or that in-home health care would be refused if offered.

For Mrs Martinez (opening paragraph), the physician should discuss the availability of Medicaid and other homemaker services as an option for providing some of the basic care that she needs. A homemaker could help Mrs Martinez get up, bathe, and dress in the morning, thereby allowing the family to continue providing other ADL, IADL, and emotional support. Because the steadily deteriorating nature of Mrs Martinez's dementia will place increasing demands on her family support system, the formal assistance might help prevent the family support from becoming prematurely overwhelmed.

We should also not ignore the role of culture in the care of Latino elders. Attention to cultural values such as respect, the involvement of family members in health decisions, and use of the Spanish language have been shown to be important aspects of the quality of care for Latinos.[21,44,45] Attention to culture should not divert health care professionals from ensuring that older Latinos have the opportunity to receive in-home health services when their physical condition merits it. For Mexican-American elders especially, who face the most structural barriers to the receipt of care, physicians should make an effort to ensure access to needed visiting nurse, home health aide, and homemaker services.

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* * *

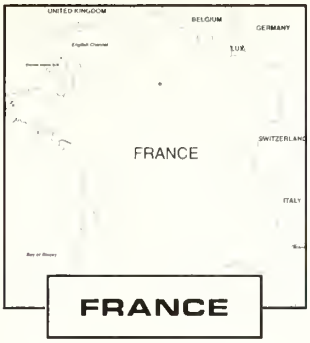
IN APRIL, HEARING THE NEWS

it's before being
a hostage to
loss and dying
numbs and each
word is charged
and when my mother
tells me I'm so
pretty as I see
her sit down
in Sears looking
lost then looks
up at me and
waves as she does
from the other
twin bed when I
can't tell since
she often sleeps
with her eyes
open if she's
sleeping and I
wasn't drained
from staying 11
weeks in a house
that's a cage is
full of cages as
my sister tries to
jail everything
that should breathe
before the night
mare of living
in a house in
enemy territory
was the price
for having
her still

LYN LIFSHIN©
Niskayuna, New York

Cross-cultural Medicine
A Decade Later

- French cultural ideas and greater experience with infectious disease, especially tuberculosis, lead to a conceptualization of AIDS that is different from that encountered in North America



The French Are Different
French and American Medicine in the Context of AIDS

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Medicine has often been approached as a thing apart from culture, as a uniform Western science. Within the past 10 years, we have begun to recognize that medicine is a system of beliefs and practices intrinsically linked to its larger sociocultural context. Still, it is generally perceived as uniform across North America and Western Europe. My recent research on French and American medical perspectives on the acquired immunodeficiency syndrome (AIDS) challenges this view by exploring differences in the structure of health care, the physician-patient relationship, and the conceptualizations of disease, particularly AIDS. These differences are not specific to AIDS, but the disease serves to exemplify them and to act as a medium for expressing what makes French and American medicine distinct. Global epidemics such as AIDS require both international response and cross-cultural understanding.

(Feldman J: The French are different—French and American medicine in the context of AIDS, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:345-349)

Biomedicine has been defined as an objective Western science of the chemical and physiologic functions, and malfunctions, of the human body. This is contrasted with "ethnomedicine," the healing systems of other societies, based not in biology but in culture. Within the past ten years, however, this focus has changed. Westerners have begun to recognize biomedicine, too, as a system of beliefs and practices intrinsically linked to its larger sociocultural context and as a legitimate focus of anthropologic research.[1,2] Although it is now well accepted to study differences in the biomedical practices of culturally distinct places such as Japan[3,4] or to study the differences between lay and professional health concepts,[5,6] medicine is generally perceived as uniform across the Western world, particularly North America and Western Europe. A notable exception is the research compiled by Hahn and Gaines demonstrating the heterogeneity of biomedicine, particularly across medical specialties.[7] Such direct qualitative research into medical practices is rare in France due to the resistance of physicians toward the involvement of social scientists either in clinics or in medical schools.[8] On both sides of the Atlantic, few researchers outside of Payer[9] and, more recently, Gaines[10] have explored possible medical differences between Western nations such as France and the United States. This has perpetuated the assumption of uniformity.

My recent research on French and American medical perspectives on the acquired immunodeficiency syndrome (AIDS) challenges this view. Epidemics in general, and AIDS in particular, give social scientists an unparalleled opportunity to examine the interaction of institutional practices, social values, and cultural assumptions.[11-14] Highly publicized medical research and treatment of AIDS took place in the United States and France from the beginning of the epidemic, providing an excellent opportunity for examining differences between the two countries.

During a portion of 1987 and from fall 1990 to 1991, I was a participant-observer in AIDS clinics in Paris, France, and Chicago, Illinois. As a fourth-year medical student and an anthropologist, I was able to participate fully in the activities of the clinics, including treating patients under supervision. In addition, in both countries I conducted 86 interviews with clinicians and researchers working with patients with AIDS and the human immunodeficiency virus (HIV). I discovered a wide variety of differences in the structure, values, and practices between French and US medical care.

Many of these differences are not specific to AIDS. Rather, AIDS serves to exemplify them and to act as a medium for expressing what makes French medicine distinct.

If American physicians were to enter a Paris clinic, they, like myself, would initially feel comfortable. All the tools of the trade would be present—thermometers, blood pressure cuffs, and the view box for reading x-ray films. Their French colleagues would be speaking in recognizable terms of pneumonia, blood counts, and brisk reflexes. Little by little, however, a certain uneasc would develop. Americans would notice that temperatures are taken rectally or under the arm but never orally. Drugs are almost never called by the generic name but by an entirely distinct set of trade names, including a vast number of antibiotics that American physicians never encounter. Powders and suppositories are popular drug forms, and it is the patients, not the physicians, who carry prescription pads. A routine checkup does not usually include a urinalysis. The French physicians rarely inquire about smoking habits or alcohol use.

One may well brush off these differences as "local color"—interesting but unimportant in the presence of over-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
AZT = zidovudine
HIV = human immunodeficiency virus

arching common ideas. It is through these differences in what people do and say that culture is expressed, however.[15] The expression of culture in French medicine can be found in how health care is structured, in the relationship between physicians and patients, and even in conceptualizations of health and disease, as in the case of AIDS. As our hypothetic visiting Americans would discover, nothing can be taken for granted.

Structure of the Health Care System

One of the first differences that confronted me in Paris was nationalized health care, where patients are reimbursed by Securité Sociale for 75% to 100% of the costs of care, including medication. On my second day at the clinic, a nurse-administrator asked me, "Is it true that you have people in America going without care because they don't have money?" This question was repeated many times by many people during my stay, accompanied by looks of either indignation or complete bafflement. The fact that everyone is *prise en charge,* literally "taken in charge," by the French health care system is an expression of social values, a belief in basic health care as a right, and that the state, rather than corporate groups or individual persons, is the appropriate guarantor of this right.[16]

This fundamental structural difference immediately affects the interaction between physician and patient. In sharp contrast to everyday practice in the United States, patients in France, except for foreign visitors, are never asked how they are paying for their care, and patients themselves almost never request a different medication because of concern over cost. When I asked a resident at the Paris clinic about differences between the United States and France, she replied:

> Well, I would say the first point is maybe a social point, because patients here, as soon as they get AZT (the main antiviral drug used in treating AIDS), they are 100% taken in charge by the Social Security. . . . That changes, I think, completely the relationship between the doctors and the patients.

The role of money changes the fundamental physician-patient relationship in a critical way. Carroll suggests that French attitudes toward talk of money are similar in character to American responses to talk of sexuality. Americans express repugnance toward public discussions of sexual experiences, whereas those of financial conquests are acceptable. In France, people may openly vaunt their sexual exploits, but bragging about one's wealth is considered to be in "bad taste."[17(pp128-131)] By developing a nationalized system of health care, the French are able to remove talk about money, an ambivalent and distasteful topic, from the medical encounter. What on the surface appears a mere difference in health care policy is, on a much deeper level, an essential difference in culture.

Generalists and Specialists

Another structural difference, that of the roles of generalist and specialist, is also highlighted by the approach to AIDS. Most clinicians in France are general practitioners, *médecins de ville,* who do not have hospital privileges. They have generally little power or prestige in the French medical community.[18] Specialists, including those in internal medicine, are employed by hospitals to admit patients and oversee their care and to run outpatient clinics in various specialties. Most patients with HIV infection are referred to these hospital-based specialists. Although some generalists do manage to care for their AIDS patients, they are not allowed to prescribe zidovudine (AZT). In addition, only hospital pharmacies are allowed to fill prescriptions for AZT and other AIDS-related medications.

The rules governing the distribution of AZT are set by multihospital committees made up of hospital clinicians and pharmacists. At one such meeting, a physician brought up the idea of expanding AZT-prescribing privileges to generalists. The pharmacists expressed skepticism that generalists would know how to manage the drug appropriately and concern that patients would go from physician to physician and pharmacy to pharmacy, stockpiling prescriptions for AZT. The committee finally agreed that certain generalists who "were known" to the hospital would be allowed to prescribe the drug, but patients could only obtain the medication at that hospital's pharmacy.

In this instance, AIDS serves as a vehicle for reshaping the role of the generalist physician in France while maintaining the power and high status of the specialist. It also underlines the power of pharmacists in dictating access to medications and the importance of personal ties—that is, of "being known" in the French medical community. The AIDS epidemic has reconstructed the role of the generalist. There simply are not enough specialists in France to handle the volume of cases, which in turn creates potential for expansion of the generalist role, first in AIDS care and then perhaps in other areas as well. As one general practitioner put it:

> The town doctors had always been kept apart, the general practitioner had always been someone who has not been well-seen in France. He is someone who is there to prescribe for sore throats, do certificates, but he has not . . . had a sufficient impact. . . . AIDS has come to transform somewhat this way of seeing the town doctor.

Boundaries Between Disciplines

In French medical practice, strong boundaries exist not only between generalists and specialists but also between specialties. Physicians in the Paris clinic, for example, rarely did funduscopic examinations on patients, a routine part of any physical examination in the United States. When I asked the reason, I was told that funduscopic examinations are the province of ophthalmologists and that few physicians outside that specialty were comfortable doing such an examination. When I explained that this was not the case in the United States, I was informally designated the funduscopic examination specialist for the clinic and was encouraged to help the residents practice this skill. As in so many areas of medicine, this strong differentiation, too, is changing in response to the AIDS epidemic. Given the high incidence of ocular infections in patients with AIDS, such as cytomegaloviral retinitis, the director of the clinic often encouraged his staff to do funduscopic examinations, to go beyond the boundaries of their own specialty, which was usually in infectious disease or general internal medicine.

In France, there seems to be less resistance to incorporating knowledge and procedures from internal medicine subspecialties, such as dermatology and oncology. Unlike any

US clinic I visited, for instance, nononcologist physicians at the Paris clinic supervised chemotherapy for Kaposi's sarcoma. This difference may stem from different conceptualizations of AIDS, discussed later, formed at the beginning of the epidemic.

Physician-Patient Relationships

As Americans who have had contact with French medicine invariably describe, the physician-patient relationship is paternalistic, with the physician assuming most of the control over decision making. On the surface this description appears to be accurate. The important question, however, is, "What playing out of sociocultural values is involved in the French doctor-patient relationship?" As might be guessed, it goes beyond a simple question of physicians maintaining control over patients.

The treatment of patients with AIDS provides an excellent setting in which to analyze this relationship. For example, American physicians almost invariably tell an HIV-positive patient of the diagnosis of full-blown AIDS, whereas French clinicians often choose not to do so. This was especially the case nearer the beginning of the epidemic, when few therapies existed. In 1987 a French informant explained:

> I never use the word "AIDS." I say, "You don't have AIDS," and that's the only reference I'm using for AIDS. I never say to a person, "You have AIDS." I say, "You have *Pneumocystis*." I let them do their own connections, I don't give it to them.

Another clinician remarked:

> Sometimes we may say to a patient, "You are an AIDS patient," OK? Sometimes we cannot because we feel it, I feel it, they know what it means, but they don't want to . . . hear the word, you know, because they want to hear, for example, "Kaposi's sarcoma," they want to hear "toxoplasmosis," "*Pneumocystis*," you know, but they don't want to know AIDS, OK? The word "AIDS."

The value expressed in this discourse is not one of maintaining control, or of saying "I know best," but rather of caring for the patient, of trying to ascertain what the patient may or may not wish to know. Although the issue of power is certainly involved in the control of information, it is not the sole factor. Rather, I would suggest that French physicians and patients both are tending to value the social tie over the imparting of information as the predominant feature of the physician-patient relationship, reinforced by the lack of commercial overtones seen in the American health care system.

Although exploring the physician-patient relationship specifically, Carroll notes that French people seek information on any topic differently from Americans, prizing the information gained from trusted people in a face-to-face encounter.[17] In fact, French patients often change physicians until they can establish this sense of trust with a provider.[19] In this regard, the physician-patient relationship in France takes on some aspects of friendship. A friend in an emergency such as illness is expected to take burdens off the ill person to the point of temporarily taking charge of the person's life. French physicians, by not fully informing patients of the diagnosis, are perhaps doing as a trusted friend might do.[12(pp75,76)]

In the United States, the stereotypic person with AIDS, especially as perceived by physicians, is well informed about the disease and takes an active role in the treatment, often suggesting or refusing specific therapies in accordance with his or her knowledge and desires. The French patient, in contrast, rarely questions the prescribed treatments and virtually never suggests alternatives. French physicians, unlike their American counterparts, rarely lay out several options for a patient's decision but rather recommend a path of therapy and explain the reasons for that recommendation.

In one such observed interaction, a French clinician discovered the rapid spread of a patient's Kaposi's sarcoma. The physician told the patient, "Because they are nodular lesions, you can't treat them locally [with radiation], you must use general [systemic] treatment." The physician then outlined the chemotherapy agents he favored. The patient's questions were procedural—how often must he come in; will he be able to work during this time—rather than questioning the proposed therapy itself. This example serves as an interesting contrast to an encounter between another French clinician and an American patient. When the physician informed the patient that he needed to be admitted to hospital to treat an infection, the American quickly suggested that he could receive the intravenous antibiotic therapy at home. The suggestion was not based on financial considerations, as the patient was covered by the French health care system, but as a therapeutic alternative in keeping with the patient's own desires. This sparked an uncomfortable negotiation between the two, a result of differences not only between the physician's and the patient's explanations of illness but also between French and American expectations of the respective roles of physicians and patients.

As with many aspects of medicine, the AIDS epidemic is changing the physician-patient relationship in France. Several French physicians told me that AIDS patients were more active and questioning about their treatment than other patients and that, because of AIDS, they have changed their approach to informing patients about their disease. The central issue, however, remains maintaining a relationship of trust, here underscored by a general practitioner:

> It's not like in cancer when, especially in France, people used to lie to patients, to say, "It's nothing, it's not a cancer." But with AIDS, I think it's impossible because most people that come here with AIDS have seen AIDS before. . . . So it's something new, too, because . . . people are aware. And I think . . . it's important not to lie because when you lie to people, they will never accept treatment and so on if they don't trust you. So you have to be very honest

Differences between French and American medicine are found not only in how medical care is structured or how physicians relate to patients but in how the body and its ills are constituted. These differences are subtle but telling, and the context of AIDS provides us again with a remarkable example.

Conceptualizations of AIDS

Earlier I noted that, unlike any of the American physicians, the French clinicians I met administered some types of chemotherapy themselves. This difference appears to be rooted in the history of AIDS in both countries. At the beginning of the epidemic, the vast majority of French clinicians who became involved with patients with AIDS were general internists or infectious disease specialists. Research on AIDS followed this pattern, coming out of hospital-based laboratories or basic biologic research centers such as the Pasteur Institute. In the United States, however, a considerable number of research and clinical investigators began their careers in oncology. Many well-known cancer centers have included AIDS research and treatment in their mission, such as Memorial Sloan-Kettering Cancer Center in New York City and

the Dana Farber Cancer Institute in Boston, Massachusetts.

These origins have a profound effect on how AIDS is viewed and treated in each country. One American clinician described a "turf battle" over AIDS between infectious disease specialists and oncologists. In his view the infectious disease specialists won but have ended up employing an oncologic model of the disease. Indeed, the attempts to develop a staging system for AIDS, as used in many cancers, have come mainly from the United States. Clinical trial protocols, too, are often structured like cancer treatment trials. Even AZT was first used as a cancer therapy.

In both French and American clinics, courses of treatment would be influenced by patients' symptoms, if any, and the number of $CD4^+$ lymphocytes (the cell initially targeted by HIV upon infection). In American clinics, clinicians would distinguish whether or not a patient has had an "AIDS-defining illness" according to the 1987 Centers for Disease Control criteria. In contrast, when epidemiologists asked a Paris clinic for a count of patients with AIDS as defined by the Centers for Disease Control criteria, the staff had to spend several minutes reviewing each patient's chart before deciding whether that patient indeed had AIDS. In France AIDS is consistently addressed as a continuous spectrum of disease rather than in the discrete stages of many American cancer models.

Although cancer remains a powerful point of reference for clinicians treating AIDS in France, their models of AIDS retain elements of an infectious disease paradigm. Themes of toxicity and the development of resistance to drugs, both important concepts in treating infectious diseases, are common when French clinicians speak of AIDS, especially in reference to the use of AZT. French physicians prescribe AZT for patients with $CD4^+$ lymphocyte counts of less than 200×10^6 per liter, whereas Americans begin such treatment much earlier, at 500×10^6 per liter. A medical panel convened by the French government to make recommendations about early treatment in HIV infection, commented thus on the results of US studies on AZT:

> It is advisable to remark that the mean length of follow-up in this study is only one year, that the long-term effects of treatment are unknown, and that the data on in vitro and in vivo resistance to zidovudine are also very fragmentary.[20(p5)]

Why the French emphasis on the problem of resistance? As cancer is a primary model for AIDS in America, so tuberculosis may be an unspoken model for AIDS in France. Historically the two countries have had extremely divergent experiences with and approaches to this chronic infectious disease that, like cancer, is common in AIDS patients. The American approach is to screen the population for tuberculosis by using skin tests and then to provide prophylaxis with isoniazid to those known to have had exposure. In contrast, the French have long had a high prevalence of tuberculosis—12,000 cases annually—and now vaccinate most of their population. In addition, resistance to isoniazid (nearly 5% of cases) and other therapies is not uncommon.[21]

Thus, the French experience with tuberculosis seems to inform their approach to AIDS, itself a chronic, difficult-to-treat infection. Concerned over the development of resistant strains of HIV in the population, the French intervene later in the course of the illness.

Another factor besides epidemiologic experience may be driving this difference in the treatment of both diseases—the French concept of *terrain*. Loosely defined, *terrain* is the body's overall ability to ward off disease and appears to be conceptually integral to French medicine as a whole. As Payer notes,

> It makes the French leaders in fields that concentrate on shoring up the *terrain*, such as immunotherapy for cancer. And it results in a decidedly more casual attitude toward the elimination of dirt and germs than that seen in many other countries.[9(p62)]

The concept of *terrain* appears fundamental to French medicine and perhaps fundamental to French conceptualizations of AIDS. For example, during a staff meeting at a French clinic, the director pointed out how some people become sick quickly with HIV infection while others stay healthy a long time, expressing it as a compatibility between each person's immune system and the virus. He concluded, "And there must be an immune response, because it [AIDS] is a slow disease. Otherwise, it would be like in infants, who don't have developed immune systems."

Working from the concept of *terrain*, it would thus be reasonable to emphasize the use of vaccines for both tuberculosis and, experimentally, AIDS, exposing the body to the disease agent and enabling the *terrain* to defend against subsequent infection. In this model it would make sense to let a relatively healthy *terrain* do its work as long as possible before damaging both it and the disease agent with relatively toxic drugs—as seen in the French approach to the use of AZT. Finally, immune modulators, such as diethyldithiocarbamate (DTC [Imuthiol]) and interferon, would be considered an important form of therapy, as reflected in their use early in the AIDS epidemic and continuing to a lesser extent today.[22] Thus, French biomedical models and treatment practices regarding AIDS arise out of culturally distinct conceptualizations of how the body works in response to disease.

Conclusion

Despite their differences, there is no doubt that French and American medicine share many commonalities, both being fundamentally based on a cellular-biochemical definition of disease. Although their approaches to AIDS vary, they remain for the most part mutually comprehensible, using similar therapies (such as AZT) and extrapolating from overlapping diseases of reference (such as cancer and tuberculosis). Yet, the two systems are dissimilar—in structure, social relations, and physiologic concepts. The context of AIDS not only reveals these differences but is transforming them. Gaines concludes that the two medical systems are not units of a universal empiric system but are distinct, locally influenced symbolic systems, continually being reinterpreted. (Atwood Gaines, PhD, Case-Western Reserve University, written communication, 1987). Western medicine, in turn, is not a single uniform medical system but a multiplicity of related systems, each arising out of its own cultural and historical context.

Several important clinical implications emerge from this conclusion. First, clinical practice is also cultural practice, whether in Japan, France, or the United States. Physicians across hospitals or across regions may differ in their practice precisely because they practice in different sociohistorical contexts. Second, AIDS is a global epidemic and as such requires international efforts from a variety of health care systems, including biomedicine. The nature of the disease may be defined differently among physicians from different countries, entailing extra effort on their part to reach common understanding. Treatment approaches that are both suc-

cessful and acceptable in one medical system may not be either in another system, as seen with the tuberculosis vaccine. Finally, the American physician-patient relationship, based on the cultural values of empowerment and information sharing, may not operate in other medical systems, resulting in differences in the protocols for clinical trials and in ethical issues such as informed consent. For cross-cultural understanding to occur, however, one must first recognize that difference exists. American and French physicians may speak to one another, but true translation requires not just a dictionary but an anthropologic perspective.

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- In 1989 in the US African-American infant mortality was 18.6/1,000 live births, twice the rate for other ethnic groups
- Being African American is a major risk factor for low birth weight and infant mortality, even among women who receive prenatal care

AFRICAN AMERICANS

Cross-cultural Medicine
A Decade Later

The Business of Preventing African-American Infant Mortality

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African-American women are twice as likely as women from other ethnic groups to have babies with low birth weights and to experience the loss of infant death. The problem is so endemic in black communities in Alameda County, California, that numerous programs have been developed over the past decade to reduce maternal risk factors and eliminate barriers to prenatal care. Despite these efforts, African-American ethnicity continues to be a major risk factor for infant mortality for reasons that are poorly understood. We take a critical look at 3 types of studies characteristic of infant mortality research: epidemiologic, studies that advocate prenatal care, and ethnomedical (cultural). We argue that the assumptions informing this research restrict the thinking about infant mortality and the political issues involved in how prevention programs are developed and structured. The persistent focus on maternal behavioral characteristics limits more in-depth analysis of the micropolitics of perinatal bureaucracies established in response to this ongoing crisis.

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Infants with low birth weights (preterm and small for gestational age) account for less than 10% of all live births in the United States, but the death toll among this small proportion of infants is largely responsible for the country's embarrassing international ranking of 24th in infant mortality.[1] African-American babies contribute disproportionately to the number of infants with low birth weights and infant deaths.[1]

The idea that infant mortality is an index of community health has nearly reached the status of cliché. Technologic advances enabling smaller and smaller babies to survive, however, have made infant mortality a less sensitive indicator of overall community well-being. Infant mortality can decline without any substantive changes in a community's general material, social, or health condition.[2] Most of the recent improvement in the US infant mortality is attributed to neonatal technology[3-5] and not to major successes in preventing low birth weights, its primary determinant. For African Americans, infant mortality is but a prelude to a series of alarming health and social status indicators carrying an ominous message: being black is a health hazard. National trends indicate that the reproductive and infant health status of African-American women and their babies parallels this deterioration in quality-of-life indices, despite a periodic commitment of resources to reversing the legacy of disparities that have characterized the experiences of African Americans. While we must question why the overall status of African Americans has worsened despite what some consider heroic intervention strategies, such a question is particularly relevant with regard to low birth weights and infant mortality.

The literature that explains and proposes solutions for low birth weights and high infant mortality in the African-American community is voluminous, and the institutions and bureaucracies mobilized to address the issue are extensive. Yet failure looms large (Table 1).[1,6-9] The current reproductive and infant health status of African-American women and their babies is reminiscent of levels of the late 1970s and early 1980s. We examine the low-birth-weight research, policies, and practices of the decade in which the current crisis

TABLE 1.—*Black/White* Infant Mortality, Per 1,000 Live Births*

Population	*Black*	*White (Non-Black)*	*% Change Mid to Late 1980s*	
			Black	*Non-Black*
United States				
1989†	18.6	8.1	+3.33	−8.99
1986‡	18.0	8.9		
California				
1987§	17.6	7.7-8.3	−6.87	−11.25
1984‖	18.9	8.9		
Alameda County, Calif				
1989¶	14.9	5.7	−21.16	−17.39
1988¶	18.9	6.9		

*The use of all-inclusive categories White (Non-Black) and Non-Black distorts important interethnic group differences in infant mortality by inflating the "White" rate and masking the variations in rates of ethnic groups without African ancestry. We recognize the limitations of this practice. Ethnic group misclassification is a legendary flaw in vital statistics reporting.

†From MacDorman and Hudson (National Center for Health Statistics).[1]

‡From the National Center for Health Statistics.[6]

§From the California Department of Health Services.[7]

‖From the Southern California Child Health Network and the Children's Research Institute of California.[5]

¶From the Alameda County Health Care Services Agency.[9]

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in maternal and child health is situated. As case illustrations we use Alameda County, California, and Oakland, its principal city, wherein most of the African-American women in the county who lost their babies lived. What happened there has also happened elsewhere.

Conceptual Diversity in Studies of Infant Mortality

It is well established that the antecedents of birth-weight and non-birth-weight specific mortality are multifactorial and complex.[10-13] The research generally fits into three categories: epidemiologic study, prenatal care promotion, and clinically oriented ethnomedical research. Ethnomedical studies typically deal with "folk medicine" or traditional medical beliefs and practices of cultural groups. Usually they focus on aspects of traditional medical systems that diverge from the biomedical model of disease. All of these studies, however, have important clinical and policy implications. They have the potential to challenge misconceptions and cultural biases, particularly with regard to populations overrepresented in data on poor birth outcomes. Insights can be

TABLE 2.—*Meta-analysis of Research on Infants With Low Birth Weights*

Source	*Study Type*	*Organizing Assumptions*	*Unit of Analysis*	*Proposed Solution or Conclusion*
Shiono and Klebanoff, 1986[14]	Epidemiologic	Women's prenatal behavior, sociodemographic and medical conditions	Individual	Further study of maternal risk factors
Murray and Bernfield, 1988[15]	Epidemiologic	Women's prenatal behavior and sociodemographic condition	Individual	Further study of prenatal care use determinants
Showstack et al, 1984[16]	Epidemiologic	Women's sociodemographic and medical conditions and prenatal behavior	Individual	Further study of effective prenatal care components and low birth weights
Kugler et al, 1990[17]	Epidemiologic	Women's sociodemographic condition and prenatal behavior	Individual	Further study of causes of low birth weights and infant morbidity
Lieberman et al, 1987[18]	Epidemiologic	Women's sociodemographic and medical conditions	Individual	Further study of socioeconomic status, hematocrits, and preterm births
Kleinman and Kessel, 1987[19]	Epidemiologic	Women's sociodemographic condition	Individual	Further study of low-risk black and white women's effective prenatal care components and systems
Emanuel et al, 1989[20]	Theoretic/ policy	Women's childhood and current pregnancy and sociodemographic condition	Individual	Further study of biologic mechanisms of infant mortality—keep programs for women and children
Boone, 1989[21]	Epidemiologic/ anthropologic	Women's sociodemographic and medical conditions, prenatal behavior, and cultural beliefs	Individual	Develop innovative prenatal care and targeted outreach for high-risk women, culturally relevant programs
Petitti et al, 1987[22]	Epidemiologic	Women's sociodemographic and medical conditions, prenatal behavior	Individual	Use data to plan targeted community, medical, and personal interventions
Binsacca et al, 1983[23]	Epidemiologic	Women's sociodemographic and medical conditions, prenatal behavior	Individual	Use data to focus additional services on high-risk women
Council on Maternal and Child Health, National Association for Public Health Policy, 1986[24]	Prenatal care promotion	Prenatal care and cost efficiency, women's sociodemographic condition and prenatal behavior	Prenatal care system and individual	Develop comprehensive, culturally sensitive, universal maternity care
Kotch, 1986[25]	Prenatal care promotion	Women's sociodemographic condition, prenatal care, and cost efficiency; prenatal behavior	Individual and prenatal care system	Improve social conditions of childbearing population; develop universal maternity care as part of a national health program for the US
Brown, 1985[26]	Prenatal care promotion	Women's sociodemographic and medical conditions, prenatal behavior, cost efficiency	Individual and prenatal care system	Universal prenatal care, targeted, high-risk interventions
Korenbrot, 1984[27]	Prenatal care promotion	Women's sociodemographic and medical conditions, prenatal behavior, cost efficiency	Individual and prenatal care system	Legislate expanded Medicaid benefits for low-income pregnant women
Institute of Medicine, Committee to Study Outreach for Prenatal Care, 1988[28]	Prenatal care promotion	Women's sociodemographic condition, prenatal behavior, and cultural beliefs; cost efficiency	Individual and prenatal care system	Target a culturally sensitive, high-risk-health education media campaign; eliminate financial and system barriers; universal maternity care
Smith, 1990[29]	Prenatal care promotion	Women's sociodemographic and medical conditions, prenatal behavior, cultural beliefs	Individual and prenatal care system	Health care system uncoordinated and inadequate to meet demand; target high-risk interventions with emphasis on prenatal education
Snow et al, 1978[30]	Ethnomedical	Women's sociodemographic and medical conditions; cultural beliefs and prenatal behavior	Individual	Women's cultural belief system influences use of prenatal care and compliance; health professionals need cultural sensitivity
Snow and Johnson, 1978[31]	Ethnomedical	Women's sociodemographic and medical conditions; cultural beliefs about food and prenatal behavior	Individual	Reproductive folklore about diet can help or hurt maternal and infant nutritional status; can be problematic for disseminating scientifically correct information
Johnson et al, 1978[32]	Ethnomedical	Women's sociodemographic and medical conditions; cultural beliefs about reproductive health and contraception	Individual	Reproductive folklore influences incorrect and inadequate information among high-risk pregnant patients
Snow and Johnson, 1978[33]	Ethnomedical	Women's sociodemographic condition, cultural beliefs about menstruation	Individual	Women are victims of their reproductive folklore, can influence negative health practices, compliance

gained by characterizing these studies by their governing assumptions about what causes (and ultimately prevents) low birth weights and high infant mortality, the particular variable(s) or unit(s) of analysis on which they focus, and the kinds of solutions to which the respective frameworks give rise (Table 2).[14-33]

Because the arguments and assumptions of these studies have inevitably been incorporated into intervention strategies, a careful consideration of their limitations makes it apparent why "the problem" seems so intransigent. It is difficult to try to address low-birth-weight and infant-mortality issues with public policies that are implemented through private and public bureaucracies created expressly for such purposes.

Epidemiologic Studies

Epidemiologic studies consistently show that high neonatal death rates among African Americans are due to racial differences in the birth-weight distribution.[3,4,14,19,20] Black women have a higher incidence of low-birth-weight babies that is largely attributed to, but only partly explained by, a higher frequency of risk factors.[18,19]

An important question in the epidemiology of infant mortality concerns the contribution of prenatal care to birth weight. Are the more favorable birth results among women who obtain prenatal care due to the prenatal care or because these women are different in significant ways (that affect birth weight) from women who do not receive adequate care?[34] This question stems in part from results of studies that show that African-American women have poorer birth outcomes than other women even when other well-known determinants, including prenatal care, are controlled for. Maternal sociodemographic characteristics such as age, parity, marital status, education, employment, the median income in the census tract where the woman lives, and public assistance status are conventional variables of analysis. Medical factors examined have included maternal hematocrit levels, pregnancy complications, infections, the number of previous spontaneous and therapeutic abortions, and preexisting diabetes mellitus. Medical care system and maternal behavioral factors such as hospital type, prenatal care adequacy, and tobacco, alcohol, and illicit drug use have been studied, as have infant characteristics such as gestational age and sex.[14-23]

Together these variables have failed to consistently or fully account for the excess of preterm infants, low birth weights, and infant death among African Americans. These studies found that the (nonlinear) relationship between gestational age and birth weight explains 41% of the variance in mean birth weights of African-American infants.[16] They show that the number and timing (adequacy) of prenatal visits is associated with 8% of African-American infant birth weights.[16] Adequate prenatal care reduces the rate of low birth weights in term infants by 71% but has virtually no effect on the rate of preterm low-birth-weight infants.[15] Conventional wisdom about the nature of maternal risk is increasingly being challenged. Questions remain about why black:white low-birth-weight ratios[19] and preterm birth rates are significantly higher among low-risk women[18] and why only 15% of the black-white racial disparity in the incidence of low birth weights and very low birth weights is attributed to ethnic differences in prenatal care use.[15] Even when income differences are factored in and financial access to prenatal care is assured, African-American women use prenatal care later and less. They may have lower rates of neonatal death and low-birth-weight babies, but the racial disparity in the rates of low-birth-weight infants remains unchanged.[15,17]

Although several investigators acknowledge the possible bias of uncontrolled sociodemographic and cultural variables that may contribute to excess African-American infant deaths,[16,17] how they conceptualize and interpret the variables that are controlled for is equally troublesome. For example, it is common for studies to assume that health maintenance organization membership and other simple measures of prenatal care adequacy, maternal education, marital and financial status are accurate components of or sufficient controls for socioeconomic status and actual patterns of prenatal care use.[14-23] When significant and independent associations between low birth weights and African-American ethnic identity are discovered, race and measures of socioeconomic status are treated as proxies of other unidentified biologic, social, environmental, behavioral, and medical care factors thought to be more directly related to low birth weights.[14,16,19] The point here is that studies are reporting less optimistic if not conflicting evidence about how much prenatal care can reduce the wide disparities between ethnic groups in rates of low birth weights and that eliminating financial barriers does not reverse the pattern of underuse of prenatal care by African-American women.

This inability to identify specific population-level causes of the large ethnic differences in low birth weights and infant death rates has led some investigators to focus on historical factors particular to African-American women. Experts give little credence to a historical model that relies on genetics or inheritance as a major determinant of black low birth weights because normal biologic interethnic group variation in birth weights is not of the magnitude to produce such substantial differences in the birth weight distribution and rates of infant death[15,19,20]; black infants with low birth weights tend to have comparable or higher survival rates than white infants of the same weight[19,35]; infant mortality due to congenital anomalies is the only cause of death in which an excess among African Americans does not occur[36]; over time the reproductive performance of immigrants from countries with high infant mortality tends to take on more favorable patterns of the host country[36]; and the overwhelming weight of the national and international evidence implicates social, behavioral, or environmental causation.[2,18,19,35,37,38]

Emanuel and co-workers ask, what about the lives of African-American women is hazardous to fetal and infant health?[20] Drawing mainly from research in Great Britain, they argue that the answer lies in the maternal childhood environment and the environment in which a woman's pregnancy occurs, that a woman's stunted intrauterine growth and body size reduce internal or reproductive organ development. Unfortunately, the intergenerational low-birth-weight thesis suffers from inattention to qualitative differences between generations, social and biologic reductionism, and recycled dichotomous variables like urban and rural, Southern and Northern. The larger issue, however, is not urban or rural, or Northern or Southern, but how and through what processes are the social, biocultural, and political realities of African-American women manifest in different pregnancy outcomes?

Boone's case-control study of black infant mortality in Washington, DC, unites epidemiology and anthropology in

an attempt to clarify the importance and interaction of many social and medical risk factors.[21] Boone rejects the "culture of poverty" thesis in favor of a shallow explication of African-American women's negative attitudes about men, their failure to articulate a "visualized household," and the absence of notions about shared (conjugal) child rearing. She hypothesizes that this group of disadvantaged women lacked a connection between male-female interactions and pregnancy and childbirth.

Because epidemiologic studies assume that the behavior of individual women is largely responsible for birth outcomes, even when they explore the societal dimensions of such behavior, the logic of their arguments leads them to advocate transforming the life-styles and beliefs of high-risk women until they show what is deemed to be acceptable behavior. Moreover, other than brief references to demographic traits or trends or to poverty, they rarely question why, let alone analyze how, it is that African-American women have become so poor and at high risk in the first place.

Studies Advocating Prenatal Care

Despite conflicting research findings about how much prenatal care contributes to reducing the wide ethnic group disparity in infant death rates, there is considerable consensus about its importance in preventing low birth weights.[3,26] Like Boone's study, much of the literature advocating prenatal care is a by-product of clinical experience and of epidemiologic and maternal and child health program studies that correlate women's use of medical care during pregnancy with better birth results. The consistent theme in this research is the cost-effectiveness or cost versus benefits to the health care system that reducing maternal risk factors will bring.[24,25,27,29] This is an important centerpiece of the policy argument for universal prenatal care.

In 1988 the Institute of Medicine identified barriers to prenatal care and recommended corrective measures.[28] The barriers included cost, inadequate program capacity, difficult and unpleasant practices that discourage women's participation, and a lack of public understanding about early prenatal care benefits. The report urged policy and program changes that would eliminate financial barriers, increase capacity with no more than a two-week wait for an appointment, and include an aggressive outreach and public information campaign targeted to specific groups. It recommended that programs have bilingual staffs, cultural sensitivity, locations accessible by public transportation, child care, more provider training, and flexible service hours. These suggestions reflect the experience and growing awareness of health professionals that financial access alone does not automatically translate into an early initiation of prenatal care.

Ethnomedicine

Cultural perspectives on maternal and infant risk in the United States can be found in clinically oriented ethnomedical research. These studies address alternative models of health and illness that coexist in different communities and often conflict with established doctrines and practices of Western medicine. In the areas of African-American reproductive health and childbirth, several articles address the clinical implications of folk medical beliefs that stem from the persistence of humoral pathology and concepts of disease etiology split into natural and supernatural domains.[30-33] Although not culturally specific to lower-class African Americans, research suggests that this cognitive framework contributes to maternal risk, late prenatal care, cultural conflict, and noncompliance in clinical settings. The pluralistic nosology of traditional black therapeutics and models of health are derived from African, Southern, Native-American, and European magicoreligious healing and medical systems.[39] Along with elements of mainstream biomedicine, this system affects the process of symptom recognition, illness labeling, and help seeking. Conflict may surface because of the types of health specialists that are consulted, different patient or physician behavioral expectations, communication styles, models of disease, and patients' resistance to invasive "high-tech" prenatal diagnostic and treatment methods.

As a corrective to epidemiologic studies where women have been matched according to similar educational levels, these ethnomedical findings are particularly instructive. They raise doubts about the validity of using educational levels for intergroup and intraethnic group comparisons that rely only on grade levels or years of education completed. Women thought to have the same educational level may differ in achievement, quality of formal education, and culturally based concepts of maternal and infant health. This applies also when education is assumed to be an acceptable proxy for socioeconomic status.

Micropolitics of Care

Although different in intent, the orientation and results of much ethnomedical research do not escape entirely the conceptual difficulties found in the epidemiologic articles and those advocating prenatal care. In all of these studies, prenatal care and the women who do or do not use it are extracted from their local political, cultural, and community contexts. Possible relationships between a community's pattern of low birth weights and the micropolitics of prenatal care have not received the scrutiny they deserve. What services are rendered, who provides them, and how they are perceived by both women who refuse and who use them are the key questions.[40]

The political dimensions of prenatal care are typically discussed at the macro level—that is, inadequate prenatal care program funding, insufficient media campaigns promoting prenatal care, the lack of a national health insurance program, and the need for policies and mandates to ensure greater, if not universal, access to prenatal care. Once again, even when system barriers to prenatal care are derided, the explanatory models do not attend to the micropolitics of institutional arrangements and the guiding assumptions of prenatal care outreach, content, and service systems. Rather, they focus on some alleged deficiency inherent in the "high-risk" target population and often imply that the cultural belief systems or a lack of values associated with poverty encourage high-risk behavior. As such, these cultural deficiencies discourage the adoption of preferred "scientific" beliefs, domestic living arrangements, and health behavioral practices presumed to differ from dominant societal and cultural values. The logical response is to encourage cultural transformation, even if sensitively masked as "appreciating diversity." Implicit in this response is the idea that African-American pregnant women, not societal institutions, are most in need of transformation. As "diversity" has become

the cultural buzzword of the late 20th century, except for ethnomedically oriented, reproductive health-related studies in medical anthropology, in practice, the concept of "cultural sensitivity" in prenatal health services for African-American women is undefined. If specified, it is implicitly reduced to having black, same-sex service professionals with some experience working with African-American low-income populations. For more in-depth clinical perspectives on culturally appropriate assessment, diagnosis, and treatment of African Americans, it is helpful to consult the literature in African-American ethnopsychology and mental health.[41-46]

Brief History of Alameda County's Perinatal Programs

Alameda County has a lengthy history of providing perinatal programs, advisory committees, advocacy organizations, and prenatal care outreach. For example, between 1978 and 1992, the following organizations have formed or dissolved in Oakland, the county's principal city: the Coalition to Fight Infant Mortality, the Oakland Perinatal Health Project, the Obstetrical Access Project, and the International Child Resource Institute. Prevention-related, policy advocacy groups and direct service programs have included Birthways; the Maternal, Child, and Adolescent Health Board of Alameda County; the East Bay Perinatal Council; the Perinatal Network; the Urban Strategies Council; the Oversight Committee on Infant Mortality; the Black Infant Mortality Forum; the Healthy Infants Program; Start Prenatal Care Program; Healthy Babies Project; Precious Beginnings and Baby Yours Projects; the Birth to School Project; and the Healthy Start Program. This is an impressive list of organizations and resources—until one realizes these agencies largely engage in a form of professional bureaucratic recycling.

The chronology of several of Oakland's perinatal health advocacy and infant mortality-related projects reveals interagency and intra-agency overlap and stagnation. This overlap is evident in personnel, in stated project agendas, and in the accumulation and control of funding for community low-birth-weight and infant mortality prevention. Since about 1985, subsidized prenatal care policies and other maternal and child health advocacy and program initiatives have expanded. This reflects years of advocacy work by a community trying to reckon with the problems of crack cocaine use, the acquired immunodeficiency syndrome, and their ramifications with respect to infant morbidity and mortality. In addition, federal and state (California) health policy has been developed that more overtly emphasizes the prevention of black infant mortality. In Alameda County this has meant the emergence of new public and private nonprofit advisory and advocacy organizations, direct service, and case management programs targeted to residents of Oakland's high-risk, working-class, and impoverished neighborhoods. Has program expansion broken the cycle of overlap among agencies? Does the adoption of favored case-management program models really "personalize the relationship between pregnant women and the network of service delivery"?

The answer to both these questions is no. The landscape of various specialized target group programs has diversified and grown, creating a new array of privately and publicly funded services and prospects for client and patient referrals. These developments have produced yet another service niche: technical consultation to health care professionals to implement and understand new regulations and the formalized management of interagency professional referral and informational networks. Service providers now have state-subsidized forums for keeping up to date with one another and to systematize the advocacy for more perinatal resources.

The existence and structure of many of these programs suggest that the national trend toward cost-effectiveness and efficiency through interagency coordination, collaboration, and client case management has taken hold as a policy priority in California and Alameda County maternal and child health funded programs.[47] This affinity for networking has produced a relatively stable, if not fairly lucrative, "perinatal advocacy and service program oligopoly." The questions we should ask are, Has this oligopoly had a beneficial effect? and What is it about Oakland that has caused this oligopoly to emerge? These questions need answering because despite all these efforts, the trends of excess black low birth weights and infant mortality have not been noticeably reversed (Table 3).

TABLE 3.—*Percent Change (1978 to 1988) in Low Birth Weight and Infant Mortality in Alameda County**

Data	*African American, %*	*Non-Black, %*
Low birth weights	+26	−12
Infant mortality	+22	−26
Total mortality†	+7	−25

*From Alameda County Health Care Services Agency, 1990.[9]
†Total mortality includes fetal deaths plus infant deaths.

The conditions precipitating the emergence of this oligopoly are related to the restructuring of the economy and an increasingly impoverished and stratified African-American population.[46,48,49] Oakland's traditional economic base in transportation, distribution, and manufacturing eroded during the 1980s. The shift to a service economy increased private social service employment by 17% from its 1981 ranking as the city's eleventh largest employer to Oakland's seventh largest private industry group employer in 1986.[50,51] During this same period, the racial disparity in low-birth-weight and infant mortality rates worsened.[52]

Although beyond the scope of this article, it is worth considering in this context the history, policy changes, and political motives that link case management as a gatekeeping, service-brokering bureaucratic process with the underpinnings of the self-help movement, the privatization of public health, and decreased access to services (A. Reed, "All for One and None for All," *The Nation*, January 28, 1991, p 91).[53,54]

Problematic Assumptions

The theoretical, health policy, and practical implications of the perinatal oligopoly must be situated in the context of changes in the local political economy and the conceptual frameworks out of which the oligopoly emerged. Despite the conceptual diversity of approaches to low birth weights and infant mortality, in each category of literature reviewed, the research results remain the same. They do not bring into focus the experiences and voices of women or how families cope and survive in a society hostile to African Americans and women and indifferent to motherhood and children "Scapegoating the Black Family: Black Women Speak," *The Nation*, July 24/31, 1989, entire issue).[55-58] Conventional measures of socioeconomic status tend to homogenize

African-American diversity and obscure realities of sex, class, and ethnicity as social relationships—relationships shaped by and articulated in particular historical, sociopolitical, and cultural contexts. This diversity and its sociocultural and political determinants are not captured in the simple, nominal, discrete, or continuous variables abstracted from birth records or from interview questions constructed and interpreted by investigators unfamiliar with African-American culture.*

Studies of infant mortality in general and African-American infant mortality in particular omit the work of more than a century of African-American and feminist scholarship (M. N. Jackson, "African American Men and the Rights of Women: The Politics of Therapeutic Thinking," *Virginia Commonwealth University Voice*, February 7, 1992, p 8).[59] Most conventional analytic epidemiologic studies ignore this scholarship. Conversely, paradigms developed in the social and behavioral science literature of African-American and feminist thought have not seriously grappled with the clinical or epidemiologic literature of low birth weights. A result of this fragmentation is that socially constructed categories like ethnic identity and socioeconomic status remain suspended as proxy or surrogate variables conceptually unavailable for more in-depth analysis and explanation on their own terms. Even when alternatives are developed, often they do not stray from basic cultural assumptions that women, "people of color," and children are "problems" needing to be solved.[60-62] Faced with the task of "solving these problems," we turn to bureaucracies, expecting their supposed structural neutrality to compensate for biases inherent in these various interpretive frameworks. It is hardly surprising that they fail to do so.

The Problem With Bureaucracy

As Parenti notes, "[b]ureaucracy can be used to administer a national health program or run death camps. Much depends on the political and class context in which it operates."[63(p255)] As well, bureaucracies are plagued by problems of accountability and control, equity, efficiency, responsiveness, and fiscal integrity.[64] If "[t]he bottom line . . . is that the manner in which any bureaucracy is organized affects how well it is able to accomplish its tasks,"[65(p458)] what tasks are existing low-birth-weight and infant-mortality–prevention bureaucracies accomplishing?

The bureaucracies established in response to high African-American infant mortality are oriented toward high-risk persons rather than entire communities. The prevailing assumption is that this is a cost-effective, humane approach for rationing scarce resources in underfunded public health systems faced with escalating community health care needs. Chamberlin has argued persuasively that high-risk identification and intervention strategies have their place but that they will have little effect on the long-term incidence of maternal and child health problems because of the typical distribution of community risk.[66,67] Without primary prevention of the underlying causes, more low- and medium-risk women and families will continue to replace that small percentage of high-risk families to whom enhanced services are primarily targeted. Some of Chamberlin's suggested community-wide strategies—after-school recreation programs, school-based health and child care, comprehensive prenatal care—are taking place, but to a large degree black infant mortality interventions are still focused on high-risk women and infants. Even with these in place in a community, Chamberlin's list of preventive programs of "proven value" takes no account of the micropolitics of implementation or their unlikelihood of being funded in these days of budget crises or ever-changing program funding priorities.

Conclusion

Because the frameworks we use to understand low birth weights and infant mortality target the behavior of women as causal factors, we are reduced to the dilemma of trying to ascertain to what extent it is appropriate for government or private sector bureaucracies to intervene in women's lives. The conceptual error is not simply that the focus is disproportionately on individual behavior but on the behavior of particular individuals. Public policies inevitably benefit certain populations or control or influence individual and group behavior. Data from the 1980s reveal that public policies in the area of low birth weights and black infant mortality have yet to affect African-American women and children in ways desired or expected. The questions begged by the data then are, Why do conceptual frameworks, approaches, and policies persist despite their ineffectiveness? Who gains from perpetuating the image of African-American women as being engaged in high-risk personal behavior?

The give and take of public policy-making and the persistent specter of draconian fiscal cuts in health and human services now force those concerned about low birth weights and infant mortality to push bureaucracies to critically assess their failures, limitations, and promise. In a climate that blames women for an ever-wider range of social problems, a danger in emphasizing the personal responsibility of African-American pregnant women for their plight is in creating an ideologic climate that legitimates more repressive policies presumably crafted with the goal of reducing maternal and infant risk.[68] The expansionist tendencies of bureaucratic agencies in the low-birth-weight prevention service industry make it imperative that we pay attention to whose interests are being served in the process. In a society where "high risk" is synonymous with being African American and where the failure to meet the needs of women and children becomes a metaphor for poverty and despair, administrators, clinicians, program developers, and case managers in service bureaucracies must insist, now more than ever, that policies be both more and appropriately responsive to women and children. This is possible only when trusted but inadequate paradigms and approaches are abandoned in favor of more accurate and less reductionist models and interpretations.

*See B. P. Bowser, "African-American Culture and AIDS Prevention—From Barrier to Ally," on pages 286-289 of this issue.

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Cross-cultural Medicine
A Decade Later

Health Policy and Ethnic Diversity in Older Americans
Dissonance or Harmony?

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The rapid growth and diversity of the older population have long-term implications for health care policies in the United States. Current policies designed for a homogeneous population are increasingly obsolete. To ameliorate obstacles that handicap many ethnic minority elders and to provide equal access to adequate and acceptable health care, several factors need to be considered. Enhanced data collection and analytic techniques are needed. The effects of race or ethnicity must be separated from other biologic, environmental, socioeconomic, cultural, and temporal factors on health status and behavior. Health care professionals and organizations serving minority elders must continue to expand their advocacy efforts to articulate the findings and their concerns to policymakers. Policymakers must understand and acknowledge the implications of an increasingly diverse society and determine what will constitute adequate, accessible, and acceptable health care within continuing fiscal constraints. Program planning, implementation, and evaluation methods must be revised to meet future health care needs effectively and efficiently.

(Wray LA: Health policy and ethnic diversity in older Americans—Dissonance or harmony? *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:357-361)

[Even] as it may liberate, diversity also complicates. It calls upon society to exhibit a greater sensitivity and responsiveness to the needs of older individuals who vary widely in all dimensions . . . [and] flexibility on the part of our social institutions.[1(p183)]

Today's older population is highly heterogeneous, a virtual "symphony of cultural diversity,"[1] but the music is not always sweet. Wide differences exist in health status, income levels, education, and living arrangements, all factors that influence quality of life and public policy. The differences are even greater for the rapidly growing populations of ethnic minorities in these older age groups.[2]

Persons may be recognized as elders at widely divergent ages—as early as 40 for many Southeast Asian and Native American groups, for example. Different cultures mark entrance into older age through social changes such as becoming grandparents, retirement, or functional status, rather than chronologic age. In contrast, current health and social policies—and most available research—tend to identify persons chronologically: as younger-old (ages 65 to 74), old (ages 75 to 84), and older-old (age 85 and above).

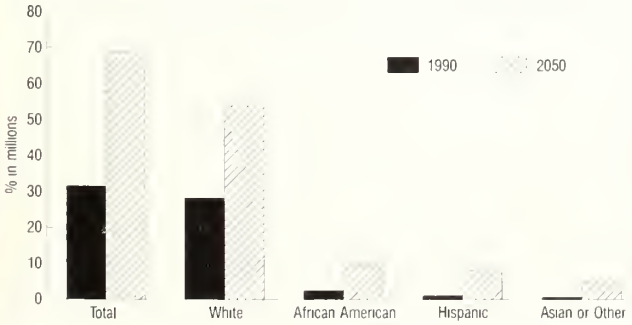

Figure 1.—The projected growth from 1990 to 2050 of persons aged 65 and older is shown by racial or ethnic group (from the US Bureau of the Census).

The population aged 65 and older in general, and elderly ethnic minorities in particular, is among the fastest growing groups in the country. In 1990, 10% of all persons aged 65 and older were ethnic minority; by 2025, 15% of the older population is projected to be ethnic minority; and by 2050, 20% will be (Figure 1).

Life Expectancy

During this century, life expectancy has improved dramatically, although unevenly, across minority and majority groups.[3] For example, in 1987 life expectancy at birth for all persons was 75 years, ranging from a low of 65 years for African-American men to 79 years for white women. While Asian and Pacific Islanders tend to have life expectancies equivalent to or exceeding whites, the higher numbers obscure considerable intragroup diversity: The life expectancy of Japanese Americans is many years higher than the life expectancy of recent Cambodian refugees, for example. The lower life expectancies for many ethnic minority groups and subgroups stem largely from their disproportionately higher rates of poverty, malnutrition, and poor health care.

Although whites are expected to live longer than African Americans at age 65, at around age 75 the reverse appears to be true. A similar pattern exists between whites and Native Americans. Researchers speculate that this "mortality cross-

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over effect" reflects a selective survival in which the least robust persons in minority groups die at earlier ages and relatively hardy ones survive to older ages.[4] In contrast, a mortality crossover does not appear to occur between Hispanics and white non-Hispanics. Data show that cardiovascular diseases contribute significantly to the mortality crossover phenomenon.[5] Higher hypertension rates may explain the higher mortality from heart disease among middle-aged African Americans and Native Americans compared with whites.[4] The data are inconsistent, however, in explaining the apparent Hispanic advantage.[6]

A 1991 study found socioeconomic status, as measured by education and net worth, to be a notable factor in health status differences between African Americans and whites older than 55.[7] When these differences were absent, African Americans and whites appear to have similar levels of health. Even after controlling for socioeconomic status, however, African Americans tend to rate their health status as lower than whites. They reported more visits to physicians but fewer hospital stays. Mutchler and Burr concluded that socioeconomic status *is* related to health care use through access—that is, in financial capacity and private health insurance coverage. Whether improvements in the overall economic status of younger and older African Americans will erase health status differences or alter the mortality crossover effect is a speculative but plausible hypothesis.[4,7] If correct, the decline since 1965 of the proportion of nonwhites living below poverty[8] may signal an increase in the proportion of middle-aged African Americans surviving to older ages.[9]

Mortality

Age-adjusted mortality by cause indicates that African Americans are more likely than whites to die of heart diseases, malignant neoplasms, diabetes mellitus, accidents, and homicides.[4,10,11] In contrast, Hispanics living in the Southwestern United States have lower age-adjusted mortality from heart disease and malignant neoplasms than do white non-Hispanics. When compared with both African Americans and non-Hispanic whites, however, Hispanics and Native Americans have higher mortality rates from diabetes and infectious and parasitic diseases. Hispanics, African Americans, and Native Americans are also disproportionately more likely than whites to die of hypertension.[11]

High rates of obesity and diabetes mellitus are characteristic of economically disadvantaged populations. Obesity is a powerful risk factor for diabetes among older African Americans and Hispanics[4,6] and may also be related to hypertension in older African Americans.[12] Diabetes and hypertension are two of the leading causes of death among African-American, Hispanic, and Native-American elders. Hispanics are generally more obese and less physically active than white non-Hispanics, are less likely to participate in lifestyles that promote cardiovascular health, and are two to five times more likely to have diabetes than the general US population.[11,13-15] Obesity alone does not explain the higher rates of diabetes among older Mexican Americans, however, suggesting that other factors, such as genetic predisposition, may be at work.[13]

Given that the same underlying disease process may trigger obesity, diabetes, and hypertension,[16] figuring out the biologic, socioeconomic, and life-style factors may help to predict, prevent, or postpone complications and develop appropriate interventions.[6]

Morbidity

Current research consistently finds socioeconomic status—as measured by income, education, or both—to be negatively correlated with levels of chronic disabilities due to disease or accidents. Given their generally lower socioeconomic status, it is no surprise that ethnic minorities have a higher prevalence of chronic disabling conditions than do elderly whites.[2,17,18] For example, Hispanics and African Americans aged 65 to 74 are likely to have a greater number of functional disabilities, as measured by restricted activity and bed-disability days, than are whites of the same ages. In addition, the chronic conditions are appearing at younger ages for nonwhites than they are for whites.[18]

Injuries are a major cause of mortality, morbidity, and work loss, affecting early retirement decisions, postretirement income, and active (or disability-free) life expectancies. Further research on the epidemiology of injury and disability will help to separate the direct from the indirect effects of race or minority status—workplace opportunities such as health insurance and sick leave, for example—on injury, disability, and retirement decisions.[19]

Health Behavior

Many health problems can be either averted or modified through targeted medical, rehabilitative, or life-style interventions. A variety of factors such as cultural beliefs, social supports, or socioeconomic status may influence the use and effectiveness of such interventions, however. For example, ethnic elders may have beliefs that influence patient compliance.[20,21] A Chinese patient with symptomatic hypocalcemia may refuse to take calcium and other dairy supplements. The patient's refusal may stem from an aversion to milk—and a high rate of lactose intolerance among Asians—but a physician whose expectations derive from Western models may see the patient as noncompliant.[22]

In addition, social supports may promote positive health behaviors,[9,23-25] such as diet changes, prevention and detection screening, thus reducing the risk of certain debilitating conditions.[26-28]

A recent study examined diet, smoking, and prevention behavior among African Americans and white non-Hispanics and found that race generally did not directly predict prevention behavior. Education was found to be a significant predictor, however.[29] Follow-up longitudinal studies may discern whether targeted educational interventions reduce behavioral, and in turn mortality, differences between African Americans and whites. Similarly, analyzing racial differences in smoking behavior may account for the influence of culture and other factors, in turn fostering more effective interventions.[30]

Hispanic disadvantage for health risks prompted a 1990 study of one potential factor in that disadvantage: preventive health service underuse among Mexican-American, Cuban-American, and Puerto Rican adults. Researchers tested whether acculturation (spoken and written language, ethnic identification) and access to care (health insurance coverage, having a routine place for care, type of facility used, having a regular provider, travel time) influenced the use of such preventive care as physical, dental, and eye checkups, Papanicolaou smears, and breast examinations.[27] Results indicated that access to care, particularly having a routine place for care and health insurance, was significantly associated with

recent screening behavior. For example, Mexican Americans were found to be less likely to have health insurance and to use preventive services recently than were the other groups. Because language but not ethnic identification also predicted use, researchers interpreted language as an "indicator of functional integration" and thus an additional access rather than acculturation factor.[27]

Because access is a central health care delivery issue, a 1991 survey explored whether the often-used global measure of regular source of ambulatory care is a useful predictor of access. The data indicated that uninsured persons, those in excellent or good health, Hispanics, and African Americans were less likely to have a regular source of care, but the reasons for that likelihood varied across groups. For example, in general, low-income persons, regardless of race or ethnicity, were more likely to lack a regular source of care for financial reasons, and rural persons were more likely than nonrural persons to lack a local resource for care.[31]

Health Policy and Ethnic Diversity

In recent years we have seen increasing life expectancy and population diversity, generally improved health for the average older person (with wide differences across population subgroups), national and international economic downturns, spiraling health care costs, and changing ideas on what it means to be "older." Health policy debates in the 1980s centered on cost containment, shifting responsibility for health care from the public back to private and individual sectors, and reassessing the need for and structure of myriad

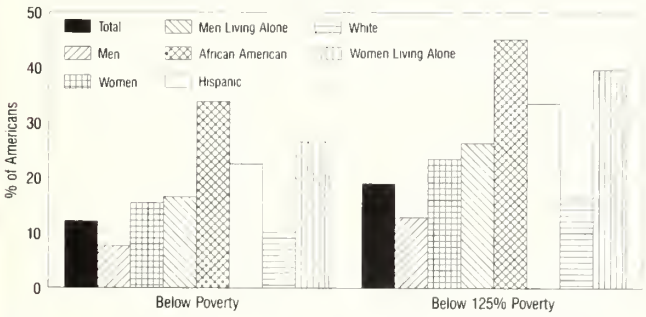

Figure 2.—The percentage of persons aged 65 and older living below the poverty line in 1990 is shown by sex, racial or ethnic group, and those living alone (from the US Bureau of the Census).

age-based health and social programs created since 1930. Whereas efficiency and costs remain priorities in the 1990s, consumers, health care professionals, and policymakers are increasingly emphasizing quality-of-care issues, including concerns about access for all.

For example, although need is the primary predictor of health services use for older persons, it is a more important predictor for minority than nonminority elders, suggesting an inherent inequality in the existing health care delivery system.[32] Redressing the inequalities requires increasing both accessibility and acceptability of health care.

Health Care Access

Available data suggest that ethnic minority elders continue to be particularly disadvantaged relative to their white counterparts on measures of socioeconomic and health status and to have a greater per-capita need for health care services, despite often lower rates of use (Tables 1 and 2). While the cause is not clear, to the extent that ethnic minority elders remain disproportionately among the poor (Figure 2) and chronically ill, policy changes, such as increased Medicare deductibles and cost sharing, have raised the "cost" of publicly funded health care to those most in need. Privately funded health care is often out of financial reach.[33] For example, although 83% of Hispanics had Medicare coverage in 1988 compared with 96% of all elders, only 21% purchased supplemental Medigap insurance compared with two thirds of all elders.[34]

In addition, the work experiences of minorities—characterized by less education, fewer occupational opportunities, and higher rates of work disability—often provoke adverse retirement experiences.[35] The work histories and citizenship status of ethnic and minority elders may have precluded jobs within the Social Security or Medicare-covered system as well. Thus, older minorities may be less adequately insured in their retirement years than are other elderly, leading some to continue working despite substantial health problems. For many older persons—particularly those older than 85 years, ethnic minorities, and women living alone—out-of-pocket health care expenses are onerous, depleting their meager resources, putting them at risk for poverty, and often forcing the choice of spending down to Medicaid eligibility levels or going without any health care.[36-41]

TABLE 1.—*Health Indicators for Hispanics, African Americans, and Whites Aged 65 and Older: National Health Interview Survey, 1978-1980**

Race or Ethnic Origin	Services Used Per Year: Physician Visits, No.	Hospital Rate, days	Dental Visit Rate, No.	Activity Limit Rate, days
All races	6.4			45.3
White†	6.3	18.3	34.4	44.3
Male	5.7			
Female	6.6			
African American‡	6.7	17.3	17.5	57.2
Male	6.3			
Female	7.0			
All Hispanic	8.2			
Mexican American	9.1	18.5	23.3	52.4
Male	9.8			
Female	8.5			
Puerto Rican	6.6	10.5	19.3	52.6
Cuban	10.8	20.3	27.9	42.1
Other Hispanic	6.2	20.8	34.7	44.4

*From Trevino and Moss.2
†Non-Hispanic.
‡Based on a small sample.

TABLE 2.—*Ethnic Populations in US Nursing Homes, by Age, 1980**

Age, yr	African American, %	Hispanic, %	Asian or Pacific Islander, %	Native American, %	White, %
65 and older	3	3	2	4	5
85 and older	12	10	10	13	23

*Based on US census data on institutionalized populations, American Association of Retired Persons Minority Affairs Initiative, 1987

Health Care Acceptability

Older ethnic minorities are currently underrepresented in nursing homes (Table 2), tending to rely instead on informal

support systems for their care. Whether this reliance is due to an extended family orientation or that ethnic minorities "care for one's own,"[42] economic constraints, or other reasons is not firmly established. Available research suggests that many ethnic families are limited in their ability to care for their older members to the extent they may desire.[43] Most older persons, whether minority or nonminority, prefer home- or community-based long-term care to institutions. The latter dominate current health care policies and programs, however.

Although changes in mortality, fertility, marriage, and divorce levels will increase the probability that in the future older persons may have surviving children or spouses, the mere existence of family members does not guarantee their availability as care givers.[44] Thus, given the lack of noninstitutional long-term care benefits, families with limited resources who may want to care for their elderly at home may be particularly burdened economically.

Health care data indicate that more rather than fewer older persons are returning home earlier from formal health care settings (although not necessarily healthier) after a major illness, that African Americans and Hispanics tend to underuse preventive services and delay seeking care until advanced stages of their conditions, and that the prevalence of chronic rather than acute conditions is associated with increasing age and socioeconomic as well as minority status. Sociologic data document that minority populations have benefited from increased life expectancy but remain at a disadvantage relative to nonminorities; that expectations regarding aging, health, and appropriate illness behavior vary across the older population; and that ethnic minority elders have historically been cared for in home environments to a greater extent than have nonminority elderly. Health care locus differences have been attributed to informal networks that encourage the use of, or act as substitutes for, formal services,[45-48] as well as differential opportunity costs and language barriers.[26,27,49]

To the extent that equal access to and acceptability of adequate health services for all persons is acknowledged as an important investment in this country's future, a health care system that provides preventive, acute, and chronic care for all throughout life is important. While health care delivery remains two-tiered, however, increased access to and acceptability of health services may be fostered by uncapping the number of Medicare-reimbursed physician visits; reimbursing for preventive health care services, patient and family education, and often-expensive medications; standardizing Medicaid eligibility requirements and increasing minimum services across states; moving away from the traditional institution-based acute care model and toward a flexible, accessible, and acceptable community- or home-based chronic care model[50]; strengthening community efforts such as counseling, information, and referral to encourage families to use available services and to provide nonfamilial support—respite, adult day care[42]; designing program criteria and procedures that do not bar participation because of immigration status or language of choice; and using functional rather than chronologic age as a measure for health and social benefit eligibility.

In addition, health policies may be revised to increase incentives, through revisions in reimbursement policy or individual tax breaks, to provide culturally and linguistically sensitive outreach, health promotion, prevention, and chronic care services targeted to those most in need.[51-53] The availability of equitable employment and educational opportunities earlier in life may also increase access to appropriate services and, in turn, may reduce the mortality and morbidity disadvantage of minorities. Finally, research is needed to examine the effects of changes in health or functional status and economic or environmental circumstances on changes in the use and costs of health and social services.[54]

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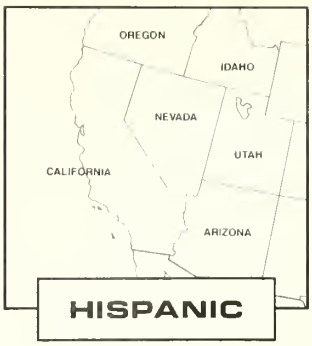
- In contrast to other parts of the US and contrary to widespread belief, California agriculture has become more, not less, dependent on migrant labor in the past few decades
- In 1989, about 1 million seasonal and migrant workers labored on California farms



Cross-cultural Medicine
A Decade Later

A Season in the Life of a Migrant Farm Worker in California

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There is an erroneous but widespread belief that in the past few decades California agriculture has become increasingly mechanized and reduced its need for migrant labor. Steeply increasing demand, however, for specialty fruit and vegetable crops, which are labor-intensive, has actually increased the need for migrant workers, who come mainly from Mexico. A case study of a young migrant describes the dismal work, economic, and living conditions such workers typically endure and the possible health consequences of those conditions.

(Palerm JV: A season in the life of a migrant farm worker in California, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:362-366)

Contrary to the widespread belief that agricultural mechanization and modernization have effectively eliminated the need to employ large numbers of low-wage seasonal farm workers, California continues to rely on the presence of a large and growing number of farm workers who work for extremely low wages and live uncertain lives. The implications for health care services and policies are substantial.

An Illustrative Farm Worker's Season

I met Pedro* in mid-September 1989, while observing a Valencia orange harvest crew at work in the vicinity of Fillmore, California, during the course of field research for the Employment Development Department.[1] A crew of 32 pickers was working an old terraced and gravity-irrigated orange grove situated on a hillside. Pedro was high on his 4-m (14-ft) ladder busily clipping oranges when the tree suddenly leaned over, uprooted itself, and toppled over the terrace with a big crash into an orange bin, nearly crushing a manned forklift machine. Pedro clung to his ladder but was left upside down entangled in the branches with the bulging 20-kg (50-lb) canvas bag tugging at his underarm. A few workers rushed from their trees to help him and, once they saw Pedro was unhurt, had a good laugh. This was the fifth time in three days the young worker had fallen from a tree. Seeing that he was shaken, the foreman suggested that he take a half-hour rest before returning to his job.

Pedro is a single, 19-year-old worker from Valle de Santiago, Guanajuato, Mexico. He had started to work at age 14 for a local construction contractor as an errand boy and by age 17 had become an accomplished *albañil* (bricklayer). His meager earnings (7,000 pesos a day [$3.50]) as an occasional construction worker, however, hardly enabled him to provide for himself. Every week he handed over half his earnings to his mother to help with household expenses. He relied on the small *ejido* farm, managed by his father and two married brothers, for basic sustenance. Pedro shared a small room with three nephews and two younger brothers.

Pedro was envious of village friends who regularly migrated to California and brought back fine clothes, electronic goods, and cash—even occasionally a car or truck. Despite the fact that no one else in his family practiced seasonal migration—at least not since his father's experience as a *bracero* in the early 1960s—Pedro decided to try his luck as a seasonal farm worker in the United States. A friend supplied him with a photocopy of his papers (immigration documentation and Social Security card) for a $50 fee, assuring him that was all he needed to obtain employment. In late February 1989, after helping his father establish the winter crop, Pedro went to Tijuana with nearly 500,000 pesos ($250) in his pocket. His first experience as an undocumented farm worker was about to begin.

Following instructions given him at home, Pedro strolled unchallenged across the border and jumped a freight train just outside San Ysidro, California. After 2½ days without food, he arrived at Oxnard where he camped along with other Mexican migrants in a cardboard-and-plastic shantytown located in a dry drainage ditch that ran between the railroad tracks and a strawberry field. The day he arrived, the fields were sprayed with a pungent fungicide, and most of the shantytown dwellers stood across the tracks waiting for the smell to recede. Because he had neglected to exchange his Mexican currency for dollars in Tijuana, he was forced to strike a deal with a local convenience store merchant to buy food. Pedro changed half of his savings (250,000 pesos) for $80, well below the official exchange rate. He later learned that this store would allow him to fill his plastic bottle with tap water whenever he made a purchase. He had been syphoning foul-tasting, lukewarm water from a plastic drip irrigation line in the strawberry field.

It took Pedro two weeks to find a job as a strawberry

*Names, locations, and other identifying features have been altered to protect farm workers.

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picker. Until then, no grower or farm labor contractor had wanted to employ him because of his dubious papers. Nonetheless, as the fresh strawberry season got busier, he was finally hired, just when he was running out of money. The first days in the strawberry fields were "pure hell," according to Pedro. Not only did he have to crawl on the humid ground from 6 in the morning to 4 in the afternoon, but he was unable to produce the amount and quality of fruit the foreman demanded. Moreover, he was suffering from nagging diarrhea, which he attributed to eating too many strawberries, and a hand rash other workers explained was caused by the fuzz on the undersides of the plant leaves. Fortunately, an old man taught him how to do the work, and soon Pedro was earning more than $4.50 per hour.

After two weeks, while still camping in the shantytown and eating purchases from the convenience store—the owner now cashed his checks for a $10 fee—he was able to accumulate nearly $400. These earnings were spent in a single afternoon, however: he mailed $250 home and bought three polyester shirts, a pair of expensive running shoes, a small "boom-box" radio, a blanket, and a baseball cap—all of well-known American brand names. Following the advice of the field foreman, Pedro purchased "legitimate" papers for an $80 fee from a local counterfeiter. The acquired papers included immigration documentation, Social Security identification, and a US entry visa.

During his third week as a strawberry picker, an acquaintance in the shantytown suggested to him that because he now had "good" papers he could aspire to a better-paid job. He was sure Pedro, with his skills, could easily find employment with a local construction contractor. The acquaintance gave Pedro an Oxnard address and told him to go there the following Monday morning when the *patrón* would be waiting for him. That morning he was put to work in the backyard of a roofing company removing nails and sorting two-by-four studs and plywood sheets piled high on two large trucks. He was told that if he did a good job, he would be considered for a full-time position.

Pedro worked hard and diligently all week (10- to 11-hour days) hoping to secure a nonfarm job, which, after the strawberry experience, was more attractive to him. On Saturday morning the *patrón* drove into the backyard where Pedro was finishing the assigned task, complimented him on his work, tossed him an impressive wad of bills tightly rolled and secured with a rubber band, and drove away saying he would be calling him soon. On undoing the bundle, Pedro discovered that a single $20 bill covered 62 one-dollar bills—his total earnings for a 60-hour week amounted to $82 ($1.36 per hour). Needless to say, the abusive *patrón* never called back.

On the following Monday, Pedro returned to the strawberry fields only to discover he was not wanted or needed; the foreman severely admonished and perfunctorily dismissed him for abandoning his job. That week Pedro sought work at an Oxnard street corner but found employment for only two half-days laboring part-time for a landscaping contractor, digging trenches for a sprinkler system in a privately owned home; his total income for that week was $34. In the course of the week he met a fellow *paisano* from Valle de Santiago who told Pedro he and others were going to Bakersfield to harvest asparagus. Pedro joined a group of five other young men, caught a ride to Bakersfield for a $20 fee, and labored near Lamont for ten days cutting asparagus. The improvised work crew camped in a truck parked next to a cotton field. During these ten days Pedro earned $425, mailed $100 home, and kept the rest in reserve.

In Lamont, Pedro was hired by a farm labor contractor to harvest navel oranges near Delano. The contractor drove him to Delano, set him up in a 3-m by 10-m (300-sq ft) windowless storage shed made of corrugated metal that he shared with eight other workers and several stacks of sacks filled with what Pedro assumed to be granulated fertilizer. Because the shed lacked indoor plumbing, the employer provided the crew with a portable toilet placed next to the shed. Tap water was available from a faucet located at the side of the structure. Every morning they were transported to the orchards on the floor of a gutted van filled with tools and returned as soon as work concluded. Work was erratic: some days the crew would harvest oranges for only 3 or 4 hours (after a 1.5-hour drive to the orchards), and other days they would work 10 to 12 hours. Although the crew was paid at a piece rate, none of the workers ever completed their quota and, hence, were earning minimum wage. Moreover, the crew constantly changed workers because most workers were beginning to head north to Oregon to participate in the berry harvest. During his first orange harvest experience, lasting 12 days, Pedro earned $357 but only retained $261 because he was charged $96 for housing and transportation. He mailed $100 home and used another $100 to pay for a ride to Oregon with a group of Oaxacan migrants in the bed of an open pickup truck.

Oregon was unquestionably Pedro's worst work experience. During eight weeks he labored for ten different employers harvesting berries and cucumbers, weeding fields, and unloading trucks. He rarely worked more than six hours a day when employed, and work was often interrupted by rain or muddy fields. Although he earned $850, well over two thirds ($570) was spent on lodging, food, and transportation. He was able to mail home only $150. The Northwest, according to Pedro, was gloomy, wet, and cold, which made him morose and homesick. As a result, he explained, he went on a five-day drinking spree, engaged the services of several prostitutes, and lost practically all his earnings. With a small monetary reserve, Pedro returned to California in early August.

After an unsuccessful search for work in Salinas, Watsonville, and Gonzalez, Pedro was finally hired in Santa Maria (near Santa Barbara) as a trainee to labor in a celery harvest crew, which he later admitted was the hardest work he encountered during his trek. At first he only stapled celery boxes shut and loaded them onto a truck. Soon he was also cutting, tying, and boxing celery bundles. The foreman drove the crew hard and hardly gave the workers time to rest, claiming that sufficient rest was possible by rotating positions every hour or so (from cutter to bundler or boxer to stapler or loader). When the workers began to show fatigue and become irritable, the foreman dispensed small triangular pills that he called "pinkos" and that he claimed would reenergize the worker. (I suspect he was administering amphetamines.) One afternoon Pedro accidentally cut his hand just above the thumb as he was chopping a bundle of celery with the awkward two-edged knife. When it became obvious that the bleeding could not be stopped with a bandage, he was rushed to a local clinic. The cut was stitched closed, and Pedro was given a tetanus shot and a pain killer. The next day when Pedro showed up for work, the foreman handed him his

paycheck and fired him, warning Pedro not to make any trouble.

By late August, Pedro was back on an Oxnard street corner seeking day employment with little success; his hand was still injured and his funds were depleted. In September Pedro was finally hired to harvest oranges near Fillmore (where I met him) and had again built up his reserve to $350. At that time he was planning to remain in Fillmore until the end of the orange harvest season and then travel east to Kern County or Fresno to participate in the raisin grape harvest, although he had been warned that the raisin season was probably already under way.

In late October, Pedro arrived home at Valle de Santiago with $850 in cash, having lost his gifts and radio to Mexican border officials. Overall, Pedro was pleased with his experience and by December was planning a second "adventure." Next time, he would get his schedule right so he could go to the San Joaquin Valley in the middle of summer to pick table grapes. Pedro was calculating that if he did things right, next year he could return home with at least $2,000, maybe even a used car.

Throughout his seven-month migratory experience in 1989, Pedro earned a total of $3,248. He provided $1,350 to his Guanajuato-based household, and $1,898 was consumed by his spartan subsistence arrangements and travel. Under the best possible circumstances, his income, had he stayed home, would not have exceeded 1,120,000 pesos—under $500. The cash Pedro provided to the household enabled an older brother to advance construction of his one-room dwelling and helped Pedro's father pay some pressing debts incurred by medical expenses for Pedro's baby sister.

California Agribusiness and Farm Laborers

Pedro was just one of about 1 million workers employed on California farms in 1989.[2,3] Considering the increasingly diverse makeup of California's agricultural labor force, which includes immigrants and migrants, men and women, young and old, documented and undocumented, Pedro, a single young man, is not a typical farm worker except that he is Mexican and poor. The conditions under which he worked, lived, and traveled, and the revenue he garnered, however, were unremarkable and were typical of the experiences most farm workers regularly encounter.

Pedro represents the new entry-level worker who is continually needed to restore a labor pool that suffers an exceptionally high attrition rate.[1] Aside from the well-known fact that farm workers tend to abandon farm employment whenever other jobs are available, the average productive life span of a farm worker is short—it is estimated to be only 15 to 20 years. Pedro, therefore, exemplifies the healthy, strong, young new worker whose physical fortitude will probably succumb to the drudgery of farm work before he turns 40, unless illness or serious injury shortens his career even more.

The 'Mexicanization' of California Farm Labor, 1940 to 1990

Three important events summarize the evolution of farm labor in California since the early 1940s:

- With the outbreak of World War II, the dust bowl refugees portrayed by Steinbeck in *The Grapes of Wrath*[4] were soon replaced with Mexican guest workers. The *Bracero* Program (1941 to 1964) encouraged and enabled many Mexican citizens to seek seasonal employment on California farms. As a result, they soon became the principal, if not exclusive, source of labor used to cultivate and harvest the state's cornucopia of crops.[1]
- Despite the euphoria and hullabaloo created by the introduction of the mechanized tomato harvester in the early 1960s—admittedly a landmark accomplishment of modern technology—most other fruit and vegetable crops have remained stubbornly resistant to mechanization.[5-7] As a result, machines never fully replaced Mexican migrant workers, who continued to supply California's steady demand, even after cancellation of the *Bracero* Program in 1964, which only had the effect of converting guest workers into undocumented aliens.[8]
- California's thriving agricultural industry, driven since the mid-1970s by a massive development of high-value fruit and vegetable specialty crops, has substantially increased its farm labor demand.[1] In other words, the growing demand for fresh fruits and vegetables brought about largely by the increased number of health-conscious consumers has greatly stimulated the agricultural industry to devote more land and capital to high-value, machine-resistant, labor-intensive, and wholesome specialty crops that, in turn, require that more low-paid farm laborers be sought to tend them. These workers come primarily from Mexico.

The process described is ongoing. For example, in the course of only five years, 1985 to 1990, Santa Barbara County farms increased average monthly employment by 62% and peak season employment by 86% (J. V. Palerm, "Farmworker Enumeration, Santa Barbara County: A Preliminary Report," Center for Chicano Studies, University of California, Santa Barbara, 1992) by substantially augmenting acreage devoted to, among other crops, broccoli, celery, lettuce, and strawberries.[9] There are, as a result, more farm workers in California than ever. What we have witnessed over the past years is not the mechanization but rather the "Mexicanization" of California agriculture.

Enclave Formation

Not all farm workers are migrant. Many have settled down permanently with their families in small rural towns and communities located in those regions subjected to agricultural intensification where farm employment is more abundant and regular. For example, in the course of the past three decades—1960 to 1990—the population of Guadalupe, a small rural California town, grew from 3,225 to 5,479 and its Mexican-origin population swelled from 18% to 83%.[1] Field research has uncovered the existence of at least 150 other rural locations where enclave formation is well under way. In some, pre-enclaves, the process is only in an embryonic stage, but in many others, majority enclaves, the process is complete. Table 1 provides some striking details about these burgeoning Mexican enclave communities of California that, in sharp contrast with the rest of rural America, are peopled by young families with extremely high fertility rates.[10]

Unfortunately, the vast majority of these settled farm-working families earn so little that their annual income only rarely reaches or exceeds the government's definition of poverty. They often crowd into substandard houses located in bankrupt communities that are unable to provide basic public services, and they are subjected to widespread neglect on the

part of most public and private social service organizations. The communities, in effect, are pockets of severe and enduring poverty that require urgent public attention.[11] Despite the bleak circumstances under which they live, few families are currently prepared to trade rural jobs and homes for urban employment given the prevailing conditions of city blight compounded with high rates of unemployment, crime, drugs, and violence.

Migrants often compete with settled workers for farm jobs. They unintentionally help to keep wages depressed and further affect overcrowded resource-poor communities during their sojourn.

Immigration Policies

The Immigration Reform and Control Act of 1986 was intended to stem the flow of illegal migrants. It has not affected California agriculture because, among other reasons, farm employers were successful in introducing special provisions that protected their growing multibillion-dollar industry—that is, the Special Agricultural Worker and Replenishment Agricultural Worker programs.[12] The main contributions of the immigration reform act, on the contrary, have been to provide an opportunity for many former and new undocumented workers to become legal and to create the perception that new legalization opportunities will be forthcoming for those who either did not qualify the first time around or who joined the labor pool later. Although the Immigration and Naturalization Service estimated that only 250,000 farm workers would apply for amnesty through the Special Agricultural Worker program, 1.3 million actually did; more than two thirds were in California alone. Subsequently, an equally impressive number of workers have preregistered for the impending activation of the Replenishment Agricultural Worker program.

TABLE 1.—*Rural Californian Chicano and Mexican Enclave Communities—General Demographic Characteristics**

Type of Community	*No.*	*Latino, %*	*Median Age, yr*	*Fertility Rate/yr*	*Average No. of Persons Per Household*
Pre-enclave	26	17.3	31.7	340	2.70
Enclave	61	30.0	26.0	376	3.04
Majority enclave	61	65.6	24.3	456	3.60
California		19.2	29.9	272	2.68

*From the US Census Bureau.[10]

Armed with bona fide papers, many former migrants have decided to settle permanently in the already overcrowded enclave communities with their undocumented dependents, whereas others continue to trek back and forth without having to cross the border clandestinely anymore. Meanwhile a new cohort of prospective farm laborers without proper documentation are being inducted into the labor market.

There is no indication that the issues briefly described here will abate any time soon. Neither agricultural modernization nor immigration legislation has been capable of either diminishing California's hunger for low-wage seasonal farm jobs or deterring the massive flow of migrants and immigrants from Mexico who meet the demand. It is paramount that we acknowledge, once and for all, that these issues are endemic to California agriculture so that we can get on with the job of addressing the myriad social problems they entail, problems that can no longer be perfunctorily dismissed as trivial, transitional, and self-corrective.

Health Care Implications

Once the permanence of the situation has been acknowledged, problems of housing, occupational risk, and access to health care can be addressed.

- Among the many problems farm workers face when they settle into their enclave communities in California and during their sojourns from Mexico is poor access to basic health care services. The problem is of singular gravity for the following reasons: it involves a large and growing population; the population, mostly from impoverished rural Mexico, suffers a long history of health deprivation and neglect; people live in overcrowded, substandard, unsanitary conditions; and a large segment of this population receives exposure on numerous occasions during work to large quantities of diverse potentially toxic substances, which can—and do—result in acute and chronic health problems.
- Few farm workers have any form of health insurance. Most seasonal farm workers are inadequately protected against accidents in an industry where accidents and injury abound. Most farm workers are unware that some degree of public aid is possible, through, for example, Medicare or Medicaid (in California, Medi-Cal). When access to services is sought, often timorously, people encounter insurmountable language or cultural barriers, unintelligible paperwork, and disinterest, if not outright discrimination, on the part of public servants. Documented special agricultural workers think they are ineligible for assistance, and undocumented workers fear they will be reported to the Immigration and Naturalization Service. Thus, few actually attempt to obtain public health services even in cases of dire need.
- When illness or injury occurs, farm workers stoically and stubbornly rely on traditional or home remedies. When that fails, they make quick emergency trips across the border to affordable Mexican health practitioners and available over-the-counter drugs. Sojourners who become too sick to continue working rush back to Mexico. As a result, it is common for farm workers not to seek professional medical assistance for themselves or their ailing dependents until illness is well beyond the scope of simple treatment and physical injuries are irreparable. Because preventive medicine is practically unheard of, expectant mothers only rarely and sporadically receive prenatal care, and children's health is commonly left unattended. All this is occurring in the midst of the most modern, successful, and profitable agricultural business in the world.

In view of this large and growing but extremely vulnerable population—constantly exposed to high-risk jobs, high-risk environments, high-risk housing, and high-risk behavior—the urgent need to find solutions cannot be overstated. A two-pronged approach is vital. It is absolutely essential that the health care system be improved to deal with the specific needs of these communities and populations. It is equally essential to educate and instruct the population on health matters.

Pedro returned home safe and sound without suffering any major mishap. He was lucky, considering his life-style and the number of close calls he had. Others have not been as fortunate. It is only a matter of time, however, before Pedro,

whether as a migrant farm worker or as a resettled community member, has a medical emergency through illness or injury. Unless there is a safety net to protect him and others like him, the probability of sustaining permanent, irreparable damage is great. It is the responsibility of those who benefit from his hard work—the agricultural business, the state, and consumers of inexpensive, wholesome farm commodities—to ensure that Pedro's productive life is not prematurely shortened or wasted and that his health and the health of his family, friends, and compatriots are not unduly compromised.

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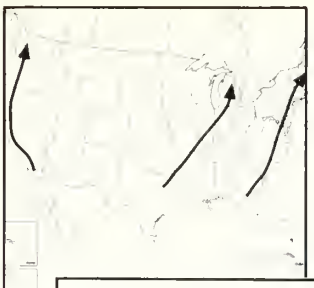
- The total population of migrant and seasonal farm workers in the US is estimated to be as large as 5 million
- In 1987, the all-cause work-related death rate (49 per 100,000 workers) for farm workers was the highest for all occupations (compared to 11 deaths per 100,000 workers for all jobs)



FARM WORKERS

Cross-cultural Medicine
A Decade Later

Occupational Health Problems Among Migrant and Seasonal Farm Workers

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Migrant and seasonal farm workers are one of the most underserved and understudied populations in the United States. The total US population of such farm workers has been estimated at 5 million, of whom about 20% live or work in California. Farm workers perform strenuous tasks and are exposed to a wide variety of occupational risks and hazards. Low socioeconomic status and poor access to health care also contribute to existing health problems in this population. Potential farm work-related health problems include accidents, pesticide-related illnesses, musculoskeletal and soft-tissue disorders, dermatitis, noninfectious respiratory conditions, reproductive health problems, health problems of children of farm workers, climate-caused illnesses, communicable diseases, bladder and kidney disorders, and eye and ear problems. Few epidemiologic studies exist of these occupational health problems. No comprehensive epidemiologic studies have assessed the magnitude of occupational health problems among migrant and seasonal farm workers and their dependents. Although the migratory nature of this population makes long-term studies difficult, the development of standardized data collection instruments for health consequences and scientific assessment of farm work exposures and working conditions are vital to characterize and reduce the occupational health risks in farm workers.

(Mobed K, Gold EB, Schenker MB: Occupational health problems among migrant and seasonal farm workers, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992 Sep; 157:367-373)

They come with the dust, and go with the wind.[1]

Agriculture is a major industrial sector in the United States and relies heavily on migrant and seasonal farm labor, especially in California where many of the labor-intensive crops, such as fruits and vegetables, are grown. Migrant and seasonal farm workers are one of the most underserved and understudied occupational populations in the US, even though they are working in one of the most, if not the most, hazardous occupations in this country.[2,3] In 1987 the three highest all-cause work-related death rates per 100,000 workers were 35 for construction workers, 38 for miners, and 49 for agricultural workers, compared with a rate of approximately 11 deaths per 100,000 workers for all occupations.[4]

The US agricultural work force was estimated in 1986 to number about 6.5 million, 5.4 million of whom lived on farms[5] and 1.1 million of whom were hired workers.[6] Migrant and seasonal farm workers are not counted separately from other farm workers by most agricultural surveys. Recent estimates indicate that as many as 5.0 million migrant and seasonal agricultural workers live and work in the US.[7] Statistics generally underestimate the dependence of agriculture on hired workers.

Among the migrant and seasonal farm-worker populations, basic health data—such as crude maternal and infant mortality, survival, and disability—are lacking, in part because of the absence of a precise denominator. This results from the transient nature of the population, their migration into and out of the US, undercounting of those workers who meet the legal definition of a migrant but who do not fit ethnic and demographic stereotypes or occupational classifications, and the desire of many immigrant workers to avoid contact with government agencies.[8] Language barriers, the seasonal nature of the work, and the large distances between camps or farms in rural, often remote, areas create further difficulties in obtaining reliable data on this population.

There is no uniform definition of migrant and seasonal farm workers among government agencies. The US Departments of Agriculture, Labor, Health and Human Services, and Education all use different standards for counting the farm-worker population, making data across agencies not strictly comparable. Currently the only national reporting system that tracks farm worker health data is the Migrant Student Record Transfer System maintained by the Office of Migrant Education of the US Department of Education. This computerized system contains the health and academic records of children of migrant farm workers in the US and Puerto Rico, but there exists no such collection of national health data on adult farm workers.[9]

Background

Agricultural labor in the United States began in the plantation days, when imported slaves worked the cotton, sugar cane, and tobacco fields of the southern states. With migra-

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tion to the West and the cultivation of vast agricultural lands in the second half of the 19th century, the need for farm help grew rapidly. First Chinese, then Japanese, East Indian, and Filipino laborers were imported to work the fields on the West Coast. During the late 1920s and until World War II, many "dust bowl migrants" from the Midwest replaced the traditional non-white farm laborers in California and other western states. With the beginning of World War II, many of those "dust bowl migrants" left the fields to take higher paying blue or white collar jobs in the defense industries. In response to the demand of American growers, *braceros*, temporary farm workers, were imported under government contract from Mexico. During this program, which continued for more than 20 years, Mexicans worked in more than 20 states but mainly in California. At the same time, laborers from Jamaica and the Bahamas were brought in under a variety of work agreements for agricultural work from New York to California. With the end of the *bracero* program in 1964, working conditions were no longer regulated by official governmental contracts between the US and Mexico. Workers were still needed, however, and this demand enormously increased illegal immigration from Mexico to the Southwest.[10]

At present three major North-South migrant "streams" exist in the continental United States. Migrants based in southern California make up the stream that heads north to northern California, Oregon, and Washington. Others, based in Texas and Arizona, travel up the Mississippi Valley to Ohio, Michigan, Indiana, and Illinois. Still others move from southern Florida through Georgia, the Carolinas, Maryland, Delaware, and New Jersey into New York and New England.[11] These streams are made up primarily of immigrants from Mexico, Puerto Rico, Haiti, Jamaica, and Central America, as well as of indigenous Native Americans and African Americans.

California is the biggest producer state in the US for vegetables and fruit and relies heavily on migrant and seasonal farm workers for these labor-intensive crops. California's migrant labor force is estimated to be between 600,000 and 1.1 million, including dependents.[12] A substantial proportion (28%) of the farm labor work force is made up of women.[13] Many migrant farm workers and their families live in established farm worker towns and maintain strong ties to Mexico. In a recent study of Chicano and Mexican rural enclaves in California, at least 60 communities were identified to be farm worker oriented, with a population that was at least 60% Hispanic.[14]

In a 1989 study of farm-worker households in four farm-worker communities in California, 65% of the persons relied on seasonal or temporary farm jobs.[14] The gross annual household income averaged $15,203, but, considering their size (average of 6.8 members per household and 2.6 workers per household), most households actually lived below officially defined poverty levels. According to 1990 US Census figures, Fresno and Tulare counties in California house possibly the poorest farm-worker communities in California, where frequently 30%or more of the inhabitants of the predominantly Hispanic farm-worker towns live below poverty levels.[15] Many farm workers and their families live in substandard and overcrowded conditions and often lack basic sanitary facilities. At peak harvest time, when migrant and seasonal farm workers travel from one harvest site to another, temporary and makeshift shelters next to the fields are common.

Intimately intertwined with the socioeconomic and general health status of this population are health problems directly due to the occupational hazards of farm work. Occupational health problems cover a wide range: accidents, pesticide-related illness, musculoskeletal and soft-tissue problems, dermatitis, noninfectious respiratory conditions, reproductive health problems, health problems of farm-worker children in the fields, climate-related illnesses, communicable diseases, urinary tract infections and kidney disorders, and eye and ear problems.[9] In addition, general health problems, such as malnutrition, poor dental health, obesity, cardiovascular disease, diabetes mellitus, anemia, and mental disorders might exacerbate the risk of work-related diseases among farm workers and their families.[8,11]

We review critically the occupational health problems of migrant and seasonal farm workers, a population defined by its occupation. Although this is only one component of the total health picture in this unique occupational group, it is an important aspect requiring urgent attention.

Accidents

Data on work injuries are not as readily available for farm workers as for workers in other industries for several reasons. First, there are no legal injury-reporting requirements for farms, other than for those farms with 11 or more employees, which must follow the regulations of the Occupational Safety and Health Administration. Workers' compensation data for agriculture are not consistent or even widely available owing to numerous exclusions, exemptions, and loopholes in state laws. Second, agriculture is physically dispersed so that collecting data about injuries requires substantial time and money. Third, as noted previously, migrant and seasonal farm labor is not treated as a separate occupational category; therefore, national agricultural accident statistics include both farmers and farm workers in the same category.

In 1989 the National Bureau of Labor Statistics estimated the annual incidence rate of all work-related injuries among agricultural workers to be 11.7%.[16] Even by these limited data, the rate of injuries in agricultural workers was higher than for workers in manufacturing industries, where the injury rate was 10.6% in 1988.[4]

Because of the wide range of tasks performed on many different crops, migrant and seasonal farm workers receive exposure to numerous factors that contribute to injury and death. Occupational accidents in agriculture include fractures or sprains due to falls from ladders or equipment; sprains or strains from prolonged stooping, heavy lifting, and carrying; amputations, lacerations, and crushed bones and joints from tractors, trucks, or other machinery; pesticide poisoning by direct spraying or mixing; electrical accidents; carbon monoxide poisoning from running equipment in enclosed areas; and drowning in irrigation ditches.[9,17]

The most comprehensive study of farm injury morbidity and mortality is the National Safety Council's 1988 survey of 127,169 farm family members, which included 57,301 full- and part-time employees on 37,293 farms in 31 states.[18] The data base covered more than 5,753 injuries, ranging from minor to crippling to fatal accidents. The survey grouped farmers and farm workers, however. The highest work-related injury rates were reported for the age group 5 to 24

years, with a combined overall rate of 25.8 work-related injuries per million work hours. Work-associated injury fatality was relatively high for those younger than 15 years (7.4%, when only 4.3% of the combined working hours by the whole farming population was contributed by this age group) and for those older than 64 years (11.1%, with 5.5% total work-hour contribution by this age group). Agricultural machinery was the single leading source of occupational injury (17.6%), followed by animal-related injuries (16.9%). Other surveillance studies of occupational injuries and mortality in farmers and their dependents have shown similar results,[19,20] but again no distinctions were made between farmers and farm workers.

Surveillance of occupational injury in migrant and seasonal farm workers poses even greater challenges than that of farmers and permanent farm help. There are difficulties in locating and identifying farm workers and gaining their cooperation in a study after a long workday. Underreporting might also be prominent if symptoms are mild, short-lived, or both. Symptoms might be ignored by a temporary farm worker, who is fearful of losing his or her job or of being reported to immigration authorities.

In 1981 a study was done of 467 families comprising 1,888 persons in Tulare County, California.[21] An aim of the survey was to gather data on the relationship between work and health. The most frequently reported work-related health problems were injuries, which accounted for 56% of all health problems reported. Falling stacks of crates, overturning gondolas, and other accidents associated with farm machinery—forklifts and tractors—were the most frequent causes of farm accidents for those who worked with field crops. Tree accidents, which included falling down from or through ladders with bags full of fruit, caused fractures, sprains, contusions, puncture wounds, and lacerations.

Of 287 migrant farm workers studied in North Carolina, 24 (8.4%) reported an occupational injury during the previous three years.[22] Broken bones, sprains, and cuts accounted for 80% of the injuries. Vehicles or machinery caused 21% of the injuries, which often resulted in time lost from work. The relatively small number of reported injuries limits the interpretation of the results. The incidence rate of injury (8.4% for a 3-year period) is, however, probably an underestimate. The use of recall rather than surveillance strategies and the exclusion of previously injured workers from the current work force could also contribute to the underascertainment.

More population-based research is necessary to characterize fully the nature, frequency, and consequences of occupational injuries in farm workers. Most of the occupational injury categories outlined by the National Safety Council have rarely been studied in migrant and seasonal farm workers. This scarcity of data limits our understanding of work-related injuries in this population.

Pesticide-Related Illness

Pesticides are a major source of public concern because of their known toxicity, their pervasiveness in the environment, and their possible association with delayed health effects, such as cancer and adverse reproductive consequences.[23,24] Pesticides, used extensively in US agriculture, include compounds such as insecticides, herbicides, defoliants, molluscicides, nematocides, algicides, and acaricides.[25] Agricultural workers can be exposed to pesticides in a variety of ways (Table 1).[9,25,26]

Labor-intensive crops, such as fruits and vegetables, are treated extensively with pesticides. Most (more than 50%) farm workers are hired for harvesting operations, during which they might be exposed to different chemical compounds when handling and touching the foliage.[26] Pesticides are absorbed into the human body through the skin, by inhalation, and by ingestion. Exposure can result in acute systemic poisoning—abdominal pain, ataxia, nausea, dizziness, vomiting, headache, and malaise—or skin or eye problems, such as rashes, inflammation, or corneal ulceration. Chronic health problems may include chronic dermatitis, fatigue, headaches, sleep disturbances, anxiety, memory problems, and different kinds of cancers, birth defects, sterility, blood disorders, and abnormalities in liver and kidney function.[9,17,26,27]

The number of workers in the United States affected by pesticides is unknown; California and Washington are the only states with mandatory reporting of pesticide-related illnesses. In the 1987 summary document of pesticide-related illnesses in California, 372 of 1,507 (25%) reported occupational cases of pesticide illness were in agricultural field workers.[28] Even in California, underreporting is likely to occur because many of the migrant and seasonal farm workers never see a physician or are never properly diagnosed.

Little is known about the extent or magnitude of chronic health problems related to occupational exposure to pesticides. Few population-based studies of such effects exist. Although several studies have addressed the association of cancer and pesticide exposure among farmers and permanent farm help,[29-34] few population-based studies have been published about the effect of pesticides in migrant and seasonal farm workers. In California, a case study of a childhood cancer cluster,[35] a hospital record-based study of birth defects,[36,37] and a health survey[21] examined some of the effects. These investigations suggest that increased chronic health problems occur. All of these studies have been limited in size and scope, however, and have not reached clear conclusions about the magnitude of pesticide-related health effects among migrant and seasonal farm workers.

Although difficult, it is important to carry out further studies on the adverse health effects associated with pesticides among farm workers. Although cohort studies of cancer or other chronic diseases would be exceedingly difficult and costly, studies of hazardous exposures, such as case-control studies of acute exposures to pesticides, are possible and appropriate. An important problem to consider is assessing exposure. Estimates of human exposure must be considered in conjunction with results of the dose-response determination to obtain quantitative estimates of risk. Appropriately designed studies could measure pesticide residues among farm workers and compare their exposure to that in other populations. Developmental toxicity and cancer from pesticides are other important areas for assessment. Pesticides have been associated with adverse acute and chronic health effects in farmers, but much additional work is necessary to characterize the nature and magnitude of this problem in migrant and seasonal farm workers.

Musculoskeletal and Soft-Tissue Problems

Heavy physical labor contributes to a variety of musculoskeletal problems, including traumatic injuries, soft-tissue

TABLE 1.—*Opportunities for Exposure to Pesticides*

Usually an avoidable exposure	Diluting and mixing; loading into applicators; applying to crop; flagging during cropdusting
Often an unavoidable exposure	Drift; contact with residues during harvesting, weeding, pruning
Frequently an unknown exposure	Eating or smoking in field; drinking, bathing, cooking with contaminated water

disorders, and degenerative joint disease of the hands, knees, and hips.[9] Few formal studies of the risk of musculoskeletal and soft-tissue conditions have dealt with agricultural populations; none have examined this in migrant and seasonal farm workers. Published articles, however, show that farm workers are exposed to many of the risk factors associated with musculoskeletal injury. For example, occupational factors that contribute to back strain include previous back injury, heavy lifting and carrying, difficult work positions, an excessively fast work pace, whole-body vibration, and work in cold or hot climates.[38]

Farm workers carry heavy bushels and buckets of produce, often lifting them above their heads to empty into trucks. Orchard workers wear canvas bags held with straps over their shoulders that they fill with as much as 30 to 35 kg of fruit as they climb up and down ladders. Mushroom workers stand on catwalks 1.5 m high that are stretched across beds so that the workers can pick mushrooms and load and unload the beds with dirt. Farm workers also spend long hours bent over low-lying crops such as cucumbers, beans, strawberries, and squash.[9]

Only a few studies of ergonomic stress and health problems in farm labor populations exist. One study in Japan examined posture patterns and musculoskeletal problems in strawberry and eggplant growers.[39] Another Japanese study compared the overhead working posture of pear and apple workers.[40] An increased number of physical symptoms such as fatigue and pain in the lower back and shoulders and tiredness, stiffness, and pain in the neck, shoulders, and arms was reported, respectively, for the two different studies. (Statistical analyses were not presented in either article.) Swedish investigators compared the frequency of hip joint operations in the Swedish population and found that more agricultural workers (36%) underwent this operation than the general population (23%).[41]

Although no formal studies of musculoskeletal problems have been carried out among migrant and seasonal farm workers, in two different health surveys of farm workers, musculoskeletal complaints ranked second and third, 21% and 27%, respectively, of all physical problems experienced.[21,42] Future epidemiologic studies on musculoskeletal problems in farm workers should focus on changes of working conditions and equipment design needed to reduce work-related musculoskeletal symptoms and disabilities among these workers.

Dermatitis

Agriculture has consistently been identified as the major industrial division with the highest risk of occupational skin disease.[43,44] In 1984 skin disorders made up more than two thirds of occupational illnesses reported to the Bureau of Labor Statistics among crop production workers.[45] Reported rates for occupational skin disease (in California) might underestimate the actual rate by 10-fold to 50-fold.[46] Table 2 shows the agents that may affect the occurrence of dermatitis in farm workers.[47,48]

The prevalence of dermatitis in general populations has been estimated in several large studies, including some in Western Europe,[49] the United States,[50] and the Netherlands.[51] Dermatitis has also been studied in Hispanics in the United States,[52] but few data exist concerning the prevalence of dermatitis in any agricultural populations, including predominantly Hispanic California farm workers. Several outbreak investigations—related primarily to pesticides—in California and Tennessee have been reported.[53-55] California grape, tomato, and citrus workers were investigated for risk factors contributing to dermatitis.[48,56,57] These surveys found that grape workers were more likely than citrus or tomato workers to report rashes and to have contact dermatitis and lichenified hand dermatitis, possibly because of crop-specific work patterns and exposures.

The future study of specific risk factors for occupational skin disease in agricultural workers could be addressed by case-control studies. The transient nature of some skin variations, however, raises issues of selection and recall bias in this type of study. To determine actual incidence, active surveillance and prospective cohort studies are necessary. The development of standardized data collection instruments is also necessary to improve the ability to compare results between populations.

TABLE 2.—*Agents Causing or Exacerbating Dermatitis*

Environmental
UV radiation
Soil
Climate—heat, cold, wind, moisture
Zoonoses
Other physical agents, such as materials for protective devices
Chemical
Pesticides, including residues on foliage
Fertilizers
Other chemicals, such as machinery lubricants
Crop-related
Specific crop type
Specific job activities, such as hoeing
Plant materials
Personal
Hygiene
Personal allergy history
Use of protective devices

Noninfectious Respiratory Illness

Respiratory illness from agricultural exposures has been well documented.[58-60] Studies have shown increased mortality from nonmalignant lung disease[61-63] and an increased number of respiratory symptoms in agricultural workers compared with nonagricultural controls.[64-69] In one study, the relative risk for pulmonary problems among farmers was found to be 1.92 compared with nonfarming controls.[68] The distinction between nonoccupational and occupational respi-

ratory exposure, however, is most difficult to draw on farms. For example, fungi that colonize growing crops predominate in the air, both by day and by night, are dispersed during haymaking, harvesting, and other agricultural operations, and affect farm workers and other rural dwellers alike.[58]

Respiratory health problems have a complex profile: One or more specific respiratory tract problems can develop at the same time. Obstructive airway disease (such as bronchitis) caused by biologic and physical agents and occupational asthma, caused generally by organic antigens contained in dusts from plant and animal sources, are major occupational health problems for farmers and farm workers. Restrictive lung disease is a less recognized result. Although continually inhaling organic dust represents a known risk for restrictive lung disease, recent studies suggest that inorganic dusts in the agricultural workplace may be hazardous as well.[70-75] "Farmer's lung" (hypersensitivity pneumonitis), probably the best known respiratory disease of farmers, is generally associated with exposure to fungal spores in moldy hay. "Organic dust toxic syndrome" resembles farmer's lung disease but is distinguished primarily by the lack of reactivity to farmer's lung antigens and by bronchoalveolar lavage findings. Often the only significant objective findings are fever and an elevated leukocyte count.[59]

Agricultural workers also may have exposure to a multitude of potential respiratory toxins, including hydrogen sulfide, fumigants such as phosphide and phosgene, ammonia, oxides of nitrogen from decomposing silage, herbicides, and pesticides.[60]

Pulmonary function has been analyzed with prediction equations developed for several populations in the United States, and ethnicity may be an important predictor of lung function.[76-78] Despite the fact that Hispanics are one of the largest and most rapidly growing ethnic groups in the US, few studies have been done of their pulmonary function. Specifically, only one comprehensive study of respiratory health in migrant and seasonal farm workers in California has been undertaken so far.[79,80] This survey found that Hispanic farm workers in California had similar prevalences of smoking to other Hispanic populations. Grape workers in this study had reduced forced vital capacities, consistent with crop-specific agricultural exposures such as inorganic dusts, organic agents, and pesticides. Furthermore, the effect of agricultural work on respiratory disorders in this population was equal in magnitude to that of cigarette smoking.

Further epidemiologic investigations on farm workers should specifically attempt to identify activities or processes associated with increased respiratory tract symptoms. Physicians caring for agricultural workers should be alert for respiratory tract symptoms and attempt to familiarize themselves with the work in which their patients are involved. Work-site evaluations by industrial hygienists, although time consuming, may help clinicians assess exposures and provide insight for recommendations regarding treatment or preventive interventions. Longitudinal assessment of lung function in populations of exposed workers will be important to determine the persistence of changes in lung function, if any, and their clinical significance.

Reproductive Health Problems

Reproductive health problems have not been well studied in either men or women working in agriculture. Case reports of sterility or low sperm counts in men who worked in manufacturing the agricultural fumigant dibromochloropropane (DBCP) have been reported from California and from six southern states.[81,82] In general, there are little or no data on reproductive problems in male farm workers.

Female farm workers also are exposed to reproductive hazards, such as prolonged standing and bending when working at conveyor belts, hoeing, thinning, or harvesting, as well as to overexertion and fatigue, pesticides and other agricultural chemicals, and insufficient sanitary facilities in the fields. These exposures might have adverse effects on reproductive health, possibly resulting in menstrual cycle disorders, infertility, spontaneous abortion, premature birth, pregnancy complications, fetal malformation or growth retardation, cancer among offspring, or abnormal postnatal development of infants from exposure to chemicals transmitted in breast milk.[9]

Some studies have analyzed the association of occupational exposures and reproductive outcomes of women employed in different occupations, including agriculture,[83-85] although none of these large studies have been designed specifically to include migrant farm workers. In a Quebec study of spontaneous abortions, statistically significant excesses of stillbirth were noted in agricultural and horticultural workers compared with other women employed in different occupations (odds ratio 5.65, $P < .01$).[84] Prematurity and occupational activity of women were investigated in two separate studies.[86,87] The rate of premature births was higher among women with jobs requiring prolonged standing (7.7%) than those with sedentary (4.2%) or active jobs (2.8%).[86] Few population-based surveys have studied infant mortality rates in this population.[88-90] In a recent study conducted in migrant clinics in California, maternal occupation in agriculture was not significantly associated with the birth weight of infants born to Hispanic mothers.[91] In other California studies,[36,37] the relative risk (RR) of giving birth to a child with limb reduction defects was significantly elevated among women who resided in a county of high agricultural productivity compared with the general population in California (RR = 1.7, 95% confidence interval 1.1 to 2.7).[37]

Many questions remain unanswered regarding possible reproductive health problems among farm workers. Future investigations might be directed at risks for fetal loss, pregnancy complications, reduced fertility, and menstrual cycle dysfunction in this population and the degree to which these risks are modified by such factors as nutritional status and access to medical care.

Health Problems of Children of Farm Workers

Children of farm workers are exposed to hazards in various ways: by doing field work (children are legally allowed to work on farms with parental consent at the age of 12, and exemptions may be granted by the US Department of Labor for 10- and 11-year-olds to harvest potatoes and strawberries), by accompanying their parents to the fields and playing in or near the fields, by living adjacent to the fields where they work, and by having contact with family members wearing contaminated clothing.[9] Indirectly, the socioeconomic and migratory or seasonal status of the parents intensifies the health problems of these children.

The lack of sanitary facilities and the unsanitary, substandard housing contribute to the spread of communicable diseases. A lack of basic health care frequently results in these children not receiving the usual childhood vaccina-

tions. Furthermore, because family income levels are often below the poverty line, many farm-worker children suffer from malnutrition.[88] In 1989 a general health screening project was carried out on 1,717 children aged 1 through 12 years in McFarland, California, following the observation of a cancer cluster among children there.[92] Of the children screened, most (71%) were referred for at least one health problem, most commonly for vision problems (40% of referrals), followed closely by dental problems (37%) and anemia (24%).

Few studies have assessed the causes and rates of injury and fatal accidents in farm children.[20,93-95] In two studies an association was noted of childhood brain tumors and leukemia with pesticide exposure, although not necessarily among children of farm workers.[85,96]

Information on the children of farm workers and their health is limited. To make any concrete assessments and recommendations, it is essential to continue studying the health problems of these children, including the health effects of short- and long-term exposure to pesticides.

Other Important Occupational Health Problems

Migrant and seasonal farm workers have exposure to other hazards that may increase their risk of health problems: climate-dependent problems, such as heat stroke or cold shock,[97] and occupationally caused infections such as anthrax, ascariasis, encephalitis, leptospirosis, rabies, salmonellosis, tetanus, and coccidioidomycosis.[98] Sensory problems are common: eye problems, caused by irritation, infection, or injury from the wind, sun, dust or soil, agricultural chemicals, debris ejected from farm machinery, and allergic reactions to plants,[99] and hearing problems due to noise from farm machinery and cannery work.[100] A lack of proper sanitary facilities in the field and crowded and unsanitary living conditions are responsible for spreading many infectious diseases such as tuberculosis and other communicable diseases.[101] Urinary tract infections and kidney disorders also occur frequently, especially in women.[9]

Despite these risks, few population-based studies have been done to assess the frequency of occupational health problems in these workers.

Conclusion

Although a number of occupational health risks have been identified through studies of agricultural workers, many gaps remain in our knowledge of the level of exposures and magnitude of specific health risks. An investigation of occupational health risks in agricultural workers must also include a consideration of general health status and access to medical care of migrant and seasonal workers. Some of the usual approaches in occupational health investigations may not be possible in this population owing to the demographic, economic, cultural, and life-style realities of the study population. The migratory nature of this population precludes serious consideration of long-term cohort studies without enormous resources, but case-control and cross-sectional studies should be considered for some health effects.

The development of standardized data collection instruments for assessing health consequences and exposures will improve the ability to compare results between populations. The application of these instruments to agricultural workers must also distinguish between the usual "farmer" category and the large population of migrant and seasonal farm workers for the results to be informative.[23]

Farm workers, their employers, and their community leaders must be approached directly to address health issues in this population. In addition, rigorous survey sampling methods involving a complete enumeration of all types of households and living quarters of migrant and seasonal farm workers in different agricultural areas during the peak agricultural work seasons must be implemented in future studies of participants who accurately represent the larger population of farm workers. Furthermore, the different languages and cultural and demographic factors inherent in these workers must also be carefully addressed in any scientific investigation.

These approaches are necessary to obtain the cooperation of farm workers and their employers so that occupational exposures and protection as well as health consequences are accurately and completely ascertained. In addition, information about health effects should be obtained in a way that is not only culturally sensitive but also meaningful to study participants and yet comparable to that obtained through standardized instruments. Undertaking studies of occupational health risks in this population with these considerations will not only contribute to the understanding of such risks but can also further preventive efforts and lead to better health in this high-risk population. Effective prevention can reduce suffering and death and contribute to enhanced productivity in the workplace. In this way, both the employers and the employees gain.

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Poem

RAIN DANCE

In the early '70's in Austin, Texas
we had a drought. It was terrible.
Day after day, week after week,
deep into August,
the temperatures stayed in the 100's
and no rain.
Nor had there been any rain for two months
before.
A kind of madness was in the hot, desiccating
summer air.
People's temples throbbed with a rhythm echoed
in the blood.
The sun itself seemed to be throbbing.
People commented they felt like there was
a big drum throbbing in the sky
slowly driving people mad with the heat,
a drumming that would not quit.
It only seemed to grow more insistent.

Some folks got the idea that for a lark
they'd invite some Indians over from East Texas
to do a rain dance.
These weren't hippies and new agers.
These were the people who played dominos
in local bars with sagging walls,
Schlitz and Frito-Lay truck drivers
and people who danced '40's-style
at the Broken Spoke on Saturday night,
a couple who took care of the retards at the
State Hospital,
a waitress and a bored housewife whose
husband drove an MKT truck between
Austin and Temple.
So they got up the money and the Indians
came down.
They did it at the tennis courts in an apartment
complex where the State Hospital couple lived.
The drumming started in the morning and kept
going all day.
Then the Indians left and everybody had a few beers and
went home.
That night
the biggest rain that had hit Austin in 70
years broke loose from a sky
that hadn't had a cloud the day before.
People said it was a real frog strangler,
a gully washer, a house-breaker,
and wasn't it funny, they said, just the day before
those folks in South Austin the paper'd said, with
photos, had had a rain dance. Everybody laughed
and remarked what a coincidence it was.

Well, a few years passed and another drought came.
The paper said it was even worse than a few years before.
And the same madness got into the air.
Finally, those folks who'd had the Indians down before
said, just for a lark, wouldn't it be neat to invite
those Indians down again?
So, they did, and they had their dance again
and everybody had a few beers and went home.
Well, that night, a rain just like the one before came on
from an equally empty sky
and three people were killed in flash floods.
This time nobody laughed or said what a coincidence it
was.
People just sort of had a few nutty laughs and
—said nothing.
There was a story in the paper again with photos
and the author had a good laugh
and the Indians went back to East Texas.
The people who'd invited them down said
they probably wouldn't do it again.

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The Conference goal is to provide opportunities for dialogue and discussion among those responsible for meeting the special challenges of the HIV epidemic, including:

- health care providers
- hospital administrators
- social workers
- dentists
- community-based and HIV/AIDS service organizations
- public health agencies
- people with HIV/AIDS
- policy-makers
- physicians
- government and community leaders
- mental health practitioners
- pharmacists
- nurses

Plenary and workshop sessions reflecting the various levels of attendee knowledge and expertise bring attention to HIV issues in four Conference tracks:

- Policy and Administration
- Education and Prevention
- Care and Services
- Treatment

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To meet its objectives, the Conference will:

- Offer an extensive series of workshops
- Focus on the role of health care providers and common issues affecting all health disciplines providing care for HIV-infected persons
- Discuss effective models of education
- Explore current ethical, legal, administrative and policy issues
- Examine issues related to access and financing
- Present research on recent advances and issues in clinical management
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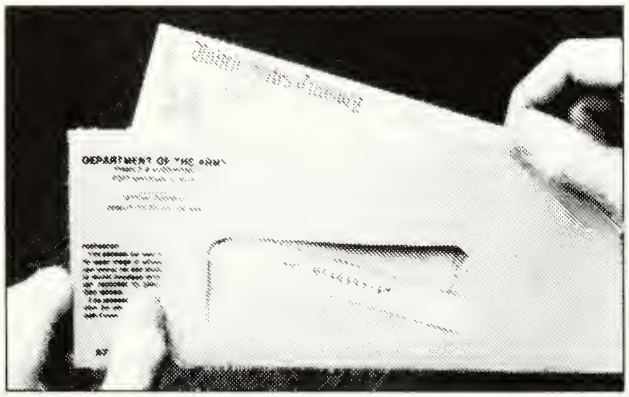

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(Continued from Page 380)

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OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

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(Continued on Page 382)

(Continued from Page 381)

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SOUTHERN CALIFORNIA. Family Practitioner needed by 20 physician Primary Care group. Several requirements have created opportunity for future partner. Generous salary and benefit package in return for commitment to quality. Location is 45 minutes east of beaches. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

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Primary Care Physicians and Radiologists needed to work as locum tenens statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **INTERIM PHYSICIANS, formerly Western Physicians Registry: Northern California, contact Jim Ellis, (800) 437-7676. Southern California, contact Tracy Zweig, (800) 635-3175.**

TWO BC/BE OB/GYNs with commitment to caring for the underserved, needed to join 13 physician (OB, Family Practice, Pediatrics, Internal Medicine), Primary Care community health clinic in Toppenish and Grandview, Washington, which has a four physician team (Family Practice, OB, Internal Medicine). Rural setting, beautiful sunny central Washington near Columbia River Gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

NEW MEXICO. Excellent opportunity for BC/BE OB/GYN, Internal Medicine, and Family Practice to join successful practices or start new in a growing community. Plan on full practice from the beginning. Enjoy sunshine, skiing, hiking, fishing, and hunting in a southwestern lifestyle. For further information on benefits and compensation contact Anne Winter, RN, Director Prof. Development, St. Joseph Healthcare System, Albuquerque, NM; (505) 246-8003.

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MONTEREY BAY. Midway between Santa Cruz and Monterey, this unpretentious community is perfect for the hiker, biker, surfer, and outdoorsperson. Medical staff is cohesive and anxious to welcome additional Family Physicians, Pediatricians, and General Internists. Group and independent practice with call schedules which allow time for lifestyle. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411, or FAX (415) 399-0411.

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(Continued on Page 383)

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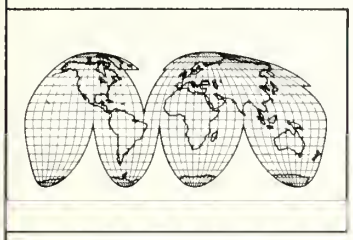

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(Continued from Page 382)

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NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through Fall of 1994. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD, EOE/M/F/V/H.

NEVADA—GASTROENTEROLOGIST. BC/BE needed to join General Intern practice in southern Nevada. Generous salary leading to full partnership. Interest in Internal Medicine preferred. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

DERMATOLOGY. BC/BE Dermatologist needed for busy Medical/Surgical practice. Located in wonderful recreational area on California's beautiful central coast. Ideal location for families, close to lake, ocean, university campus. Surgical and/or pathology skills preferred. Partnership potential. Send résumé to Number 268, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PULMONARY/CRITICAL CARE. Immediate opening for BC/BE Pulmonologist to join two BC Pulmonologists/Intensivists in expanding practice located in a desirable southern California seaside community. This outstanding opportunity provides a 100% Pulmonary/Critical Care consultative practice, academic affiliations/teaching position available locally. Please reply with a letter of introduction and CV to Number 269, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 384)

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(Continued from Page 383)

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NATIONWIDE. Urgent Care, Family Practice, and Emergency Physicians are now needed in multiple locations which include Idaho, North Carolina, Virginia, Alabama, Arizona, and more. Please send your CV to Barbara Miller, Snake River Physicians, 2995 N Cole Rd, Ste 200B, Boise, ID 83704, or call Barbara Miller at (800) 688-5008.

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(Continued on Page 385)

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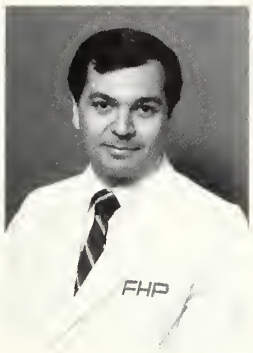

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(Continued from Page 384)

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TWO EMERGENCY OR FAMILY PRACTICE PHYSICIANS BE/BC needed to staff two clinics in Bellingham, Washington. One clinic is Primary Care; one is Ambulatory Care. No OB required. Desirable northwest location where water and mountains meet. Income guarantee. Equity opportunity. Send CV to PO Box 1644, Blaine, WA 98230.

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(Continued on Page 386)

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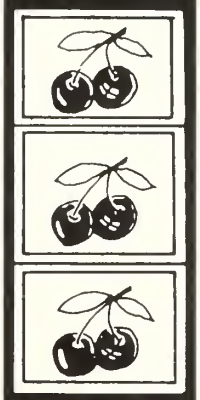

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(Continued from Page 385)

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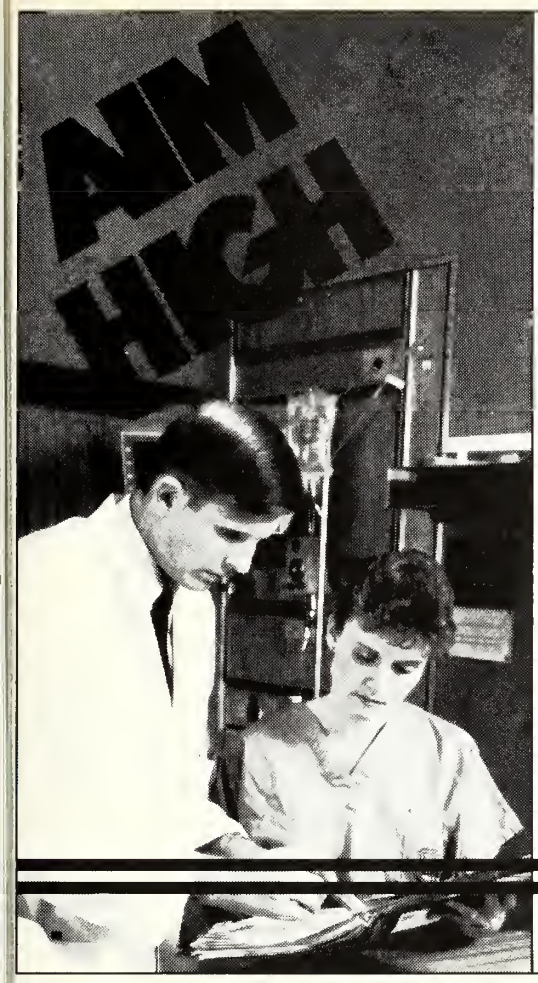
(Continued on Page 387)



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(Continued from Page 387)

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1993, date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: 1993, date and place to be announced.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1992, Honolulu.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1993, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 1-3, 1992, Bozeman.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: 1993, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: 1993, date and place to be announced.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: October 1-4, 1992, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1993, date and place to be announced.

ADVERTISING INDEX

AMERICAN MEDICAL WOMEN'S ASSOCIATION 243

BFI MEDICAL WASTE SYSTEMS 217

BLUE CROSS OF CALIFORNIA 214, 215

CALIFORNIA DEPARTMENT OF CORRECTIONS 384

CHASE MANHATTAN 235

CIGNA HEALTHPLAN 381, 383

CLASSIFIED ADVERTISING 378, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389

COLLEGE OF FAMILY PHYSICIANS OF CANADA 243

COMP HEALTH 381

DOMUS MEDICAL MANAGEMENT 245

ELI LILLY & COMPANY
Humulin 225

FHP HEALTH CARE 385

450 SUTTER MEDICAL/DENTAL BUILDING
San Francisco 377

GLAXO INC.
Zantoc ..... 3rd & 4th Covers

JOURNAL WATCH 237

KAISER PERMANENTE 385

MAAS ROWING SHELLS 377

MARION MERRELL DOW
Cordizem 229, 230

MEAD JOHNSON PHARMACEUTICALS
Buspar 245, 246

OREGON HEALTH SCIENCES UNIVERSITY 221

PALISADES PHARMACEUTICALS INC.
Yacan 233

PHYSICIANS INTERINDEMNITY INSURANCE 227

SANDOZ PHARMACEUTICALS
DynoCirc 238, 239, 240

G.D. SEARLE & COMPANY
Calan SR 219

SOUTHERN CALIFORNIA PHYSICIANS INSURANCE EXCHANGE 231

SUTTER NEUROSCIENCE CENTER 375

UNIVERSITY OF SOUTHERN CALIFORNIA
University Hospital 222, 223

UPJOHN COMPANY
Ragaine ..... 2nd Cover, 213

US AIR FORCE 387

US ARMY 383

US ARMY RESERVE 379

THE WESTERN JOURNAL OF MEDICINE
Cross-cultural Medicine—A Decade Later 220
Special Issues 226
Subscription 213

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BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within 4 weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within 1 or 2 weeks after starting therapy with Zantac 150 mg b.i.d.
6. Treatment of endoscopically diagnosed **erosive esophagitis.** Healing of endoscopically diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with Zantac 150 mg q.i.d. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with Zantac.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer, hypersecretory states, GERD; and erosive esophagitis.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and theretore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously tor 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.
Musculoskeletal: Rare reports of arthralgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day.
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

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Store between 4° and 25°C (39° and 77°F). Dispense in tight, light-resistant containers as defined in the USP/NF.

May 1992
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VOLUME 157 • NUMBER 4 OCTOBER 1992

ARTICLES

421 Tuberculosis Chemoprophylaxis
S SALPETER

425 The 10-Year Experience of an Academically Affiliated Occupational and Environmental Medicine Clinic
L ROSENSTOCK, W DANIELL, S BARNHART, B STOVER, J CASTORINA, S E MASON, N J HEYER, R HUBBARD, J D KAUFMAN, C A BRODKIN, and M KEIFER

430 Controlling a Syphilis Epidemic
D A COHEN, R SCRIBNER, and D CORY

433 Predicting Risk for Medical Malpractice Claims Using Quality-of-Care Characteristics
S C CHARLES, R D GIBBONS, P R FRISCH, C E PYSKOTY, D HEDEKER, and N K SINGHA

CONFERENCES AND REVIEWS

440 Overwhelming Postsplenectomy Infection—Still a Problem
M L BRIGDEN

444 Gastrointestinal Complications of Nonsteroidal Anti-inflammatory Drugs
R R RABB

OMES

ant Advances in Ophthalmology

RTS, NOTICES, AND CASE REPORTS

nal Death Due to Rupture of a Low Transverse Cesarean n Incision During Labor at Home
ANZARITE, E FOSTER, P ROBINETTE, L M COUSINS, and J M DER

on of *Borrelia burgdorferi* From Ticks in Southern nia
YERS, D F MOORE, G GELLERT, G L EULER, T J PRENDERGAST, II, J P WEBB, and C L FOGARTY

COMMENTARY

457 Personal Renewal
J W GARDNER

EDITORIALS

460 'New Habits of Mind'—Bridging the Gap Between Public Health and Clinical Medicine • Complications of Asplenia and Hyposplenism—Persistent Uncertainties • Treatment Strategies in the Prevention of Tuberculosis • Nonsteroidal Anti-inflammatory Drugs and Ulcers

CORRESPONDENCE

469 'What Kind of Work Do You Do?' • Cancer Screening in Women • Exaggerated Threat of Childhood Lead Poisoning in California—Epidemic by Edict • Another Health Food Hazard—γ-Hydroxybutyrate-induced Seizures • Licensing of Tissue Banks in California • Pulse Oximeter Versus Electrocardiogram • Discounting Our Future • Meta-analyses Revisited

LESSONS FROM THE PRACTICE

474 A Suitcase Full of Pills
R E WALTMAN

OTHER FEATURES

403 Instructions for Authors

410 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington

439 Poem

480 Subscription Information

481 Classified Advertising

492 Western State Medical Associations' Meetings

Detailed Table of Contents: 404, 406, 408

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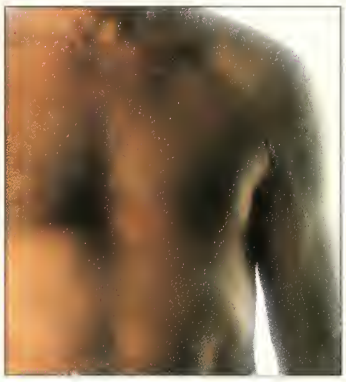

Maintains cardiac performance.

- No significant effect on heart rate*[7-10]
- No adverse effect on cardiac conduction[11,12] or contractility†[3,10,13-15]
- No alteration of digoxin clearance[16]

Does not compromise metabolic parameters.

- No clinically significant effect on serum glucose metabolism[17]
- No effect on glucose tolerance, insulin secretion or insulin action in NIDDM patients[17]
- No clinically significant effect on lipid metabolism[18,19]

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- No known contraindications except for hypersensitivity to DynaCirc
- No significant interactions with the 20 most-commonly prescribed drugs‡
- Effectively reduces diastolic and systolic blood pressure without orthostatic hypotension§[7,20,21]
- Side effects are usually minimal and transient¶[7,20-23]
  - —Low incidence of edema: 3.5% at 2.5 mg b.i.d. and 8.7% at 5 mg b.i.d.
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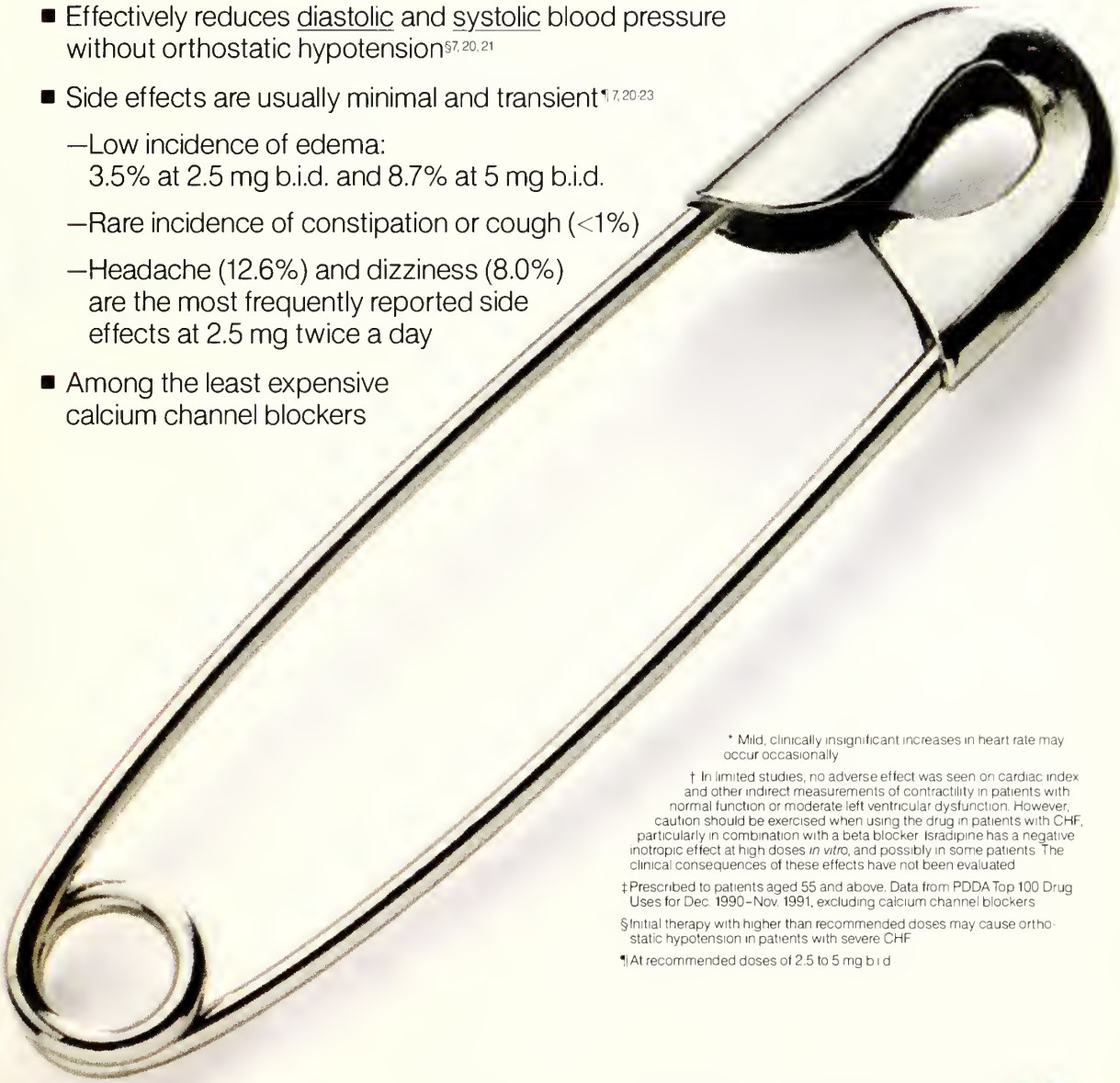

* Mild, clinically insignificant increases in heart rate may occur occasionally

† In limited studies, no adverse effect was seen on cardiac index and other indirect measurements of contractility in patients with normal function or moderate left ventricular dysfunction. However, caution should be exercised when using the drug in patients with CHF, particularly in combination with a beta blocker. Isradipine has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. The clinical consequences of these effects have not been evaluated

‡ Prescribed to patients aged 55 and above. Data from PDDA Top 100 Drug Uses for Dec. 1990–Nov. 1991, excluding calcium channel blockers

§ Initial therapy with higher than recommended doses may cause orthostatic hypotension in patients with severe CHF

¶ At recommended doses of 2.5 to 5 mg b.i.d

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2.5 mg capsules (isradipine) 5 mg capsules

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BRIEF SUMMARY
Please see package insert for full prescribing information.

DYNACIRC® (isradipine) CAPSULES

INDICATION

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None

PRECAUTIONS

General: *Blood Pressure*: Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses. *Use in Patients with Congestive Heart Failure*: Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker. **Drug Interactions**: *Nitroglycerin*: DynaCirc® has been safely coadministered with nitroglycerin. *Hydrochlorothiazide*: A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect. *Propranolol*: In a single dose study in normal volunteers coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol. *Digoxin*: The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, nonrenal and total body clearance of digoxin. *Fentanyl Anesthesia*: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. A comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats. **Pregnancy**: *Pregnancy Category C*: There are no adequate and well controlled studies in pregnant women. DynaCirc® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers**: It is not known whether DynaCirc® is excreted in human milk. A decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**: Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience. Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia), and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions (vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations, and gastrointestinal disturbances. The following adverse reactions have been reported by 1% or greater of patients receiving DynaCirc® at any dose (N=934): headache (13.7%), dizziness (7.3%), edema (7.2%), palpitations (4.0%), fatigue (3.9%), flushing (2.6%), chest pain (2.4%), nausea (1.8%), dyspnea (1.8%), abdominal discomfort (1.7%), tachycardia (1.5%), rash (1.5%), pollakiuria (1.5%), weakness (1.2%), vomiting (1.1%), diarrhea (1.1%). The following adverse events were reported in 0.5-1% of the isradipine-treated patients in hypertension studies, or are rare, but more serious events from this and other data sources, including postmarketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain. **Skin**: pruritus, *urticaria*. **Musculoskeletal**: cramps of legs/feet. **Respiratory**: cough. **Cardiovascular**: shortness of breath, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure*. **Gastrointestinal**: abdominal discomfort, constipation, diarrhea. **Urogenital**: nocturia. **Nervous System**: drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, *syncope, paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke*. **Autonomic**: hyperhidrosis, visual disturbance, dry mouth, numbness. **Miscellaneous**: throat discomfort, *leukopenia, elevated liver function tests*.

[DECEMBER 31, 1990 DYN-Z2]

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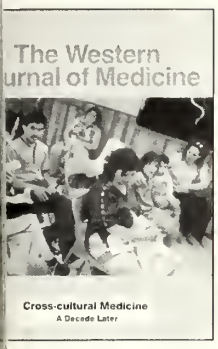

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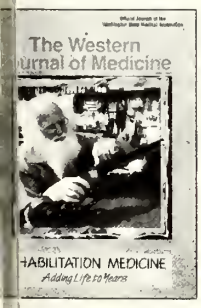

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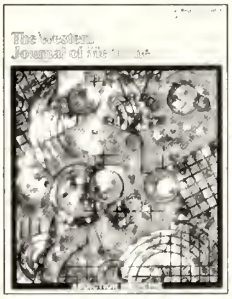

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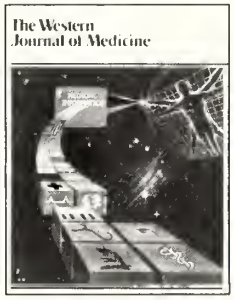

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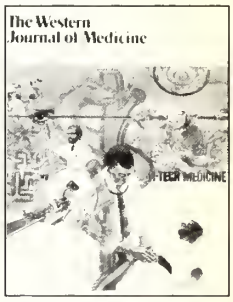

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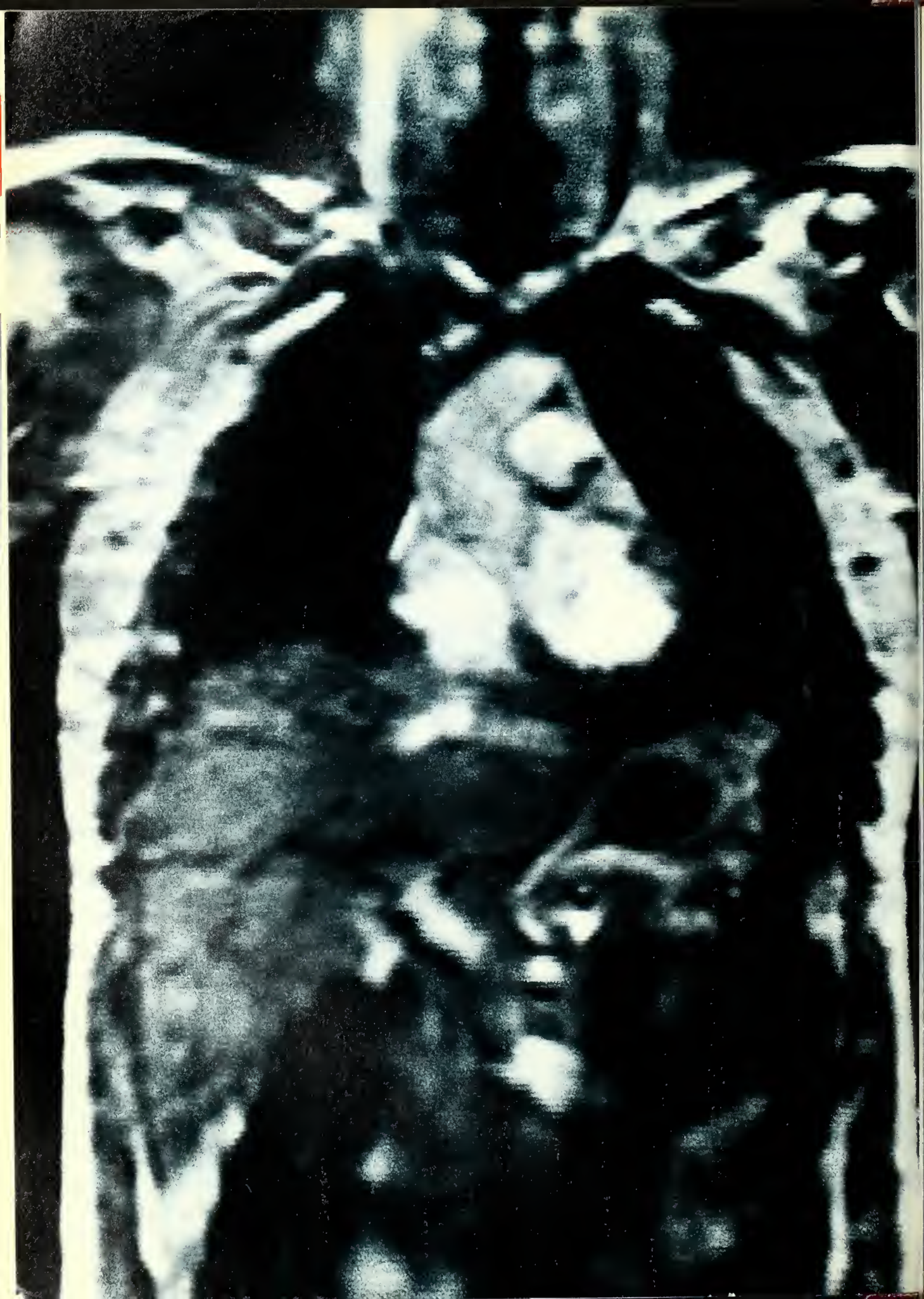

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ABSTRACTS OCTOBER 1992

(Cohen DA, Scribner R, Cory D: Controlling a syphilis epidemic. West J Med 1992 Oct; 157:430-432)

In 1986 the rate of infectious syphilis (primary and secondary) in Los Angeles County began to rise from previously stable levels of about 23.5 per 100,000 to peak at 55.6 per 100,000 in 1987. The incidence of congenital syphilis increased from 205 cases in 1987 to 575 cases in 1989. The county's Sexually Transmitted Disease Program instituted a disease-specific plan to address the epidemic. Factors considered in designing the program included the high morbidity and mortality associated with congenital infection, the existence of latent infection, self-limiting symptoms, and the availability of an inexpensive screening test and curative treatment. Policy changes implemented comprised expanded screening, expanded surveillance, increased contact tracing, and the initiation of condom promotion programs. To evaluate the relative effectiveness of Los Angeles County's syphilis control efforts, the epidemic curve for infectious syphilis was compared with trends in other urban areas. Although the rate of infectious syphilis climbed a year earlier in Los Angeles than in other cities, it returned to baseline levels when other cities' rates remained at epidemic levels.

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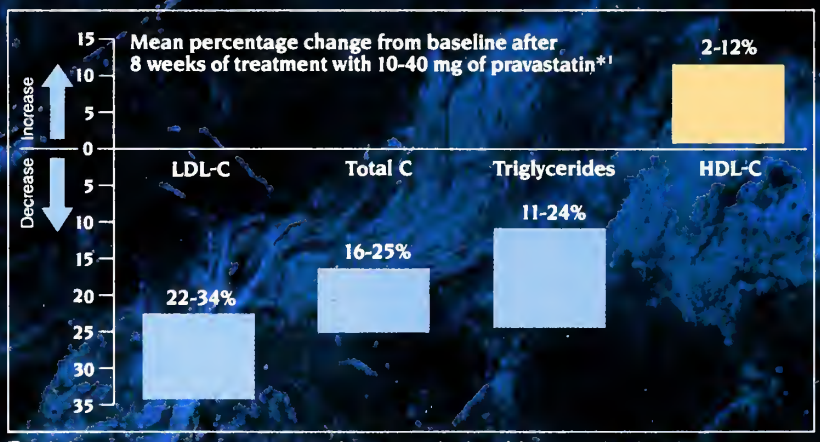

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Diarrhea	2.0	1.9
Abdominal pain	2.0	3.9
Constipation	2.4	5.1
Flatulence	2.7	3.4
Heartburn	2.0	0.7
Cardiac chest pain	0.1	0.0
Rash	1.3	0.9
Fatigue	1.9	1.0
Chest pain	0.3	0.2
Dizziness	1.0	0.5
Urinary abnormality	0.7	1.2
Rhinitis	0.1	0.0
Cough	0.1	0.0
Localized pain	1.4	1.5
Myalgia	0.6	0.0

*Statistically different from placebo.

- Discontinuation rate from pravastatin (1.7%) was not statistically different from that of placebo (1.2%)

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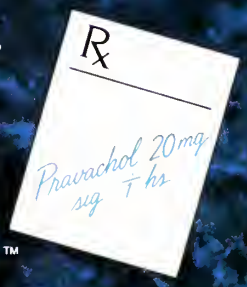

PRAVACHOL™

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References: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol* 1991;14:146-151. 2. Data on file, Bristol-Myers Squibb.

PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation: Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia: Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency: A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin*. See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid*, or *probucol*, no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to diuretics, antihypertensives, digitalis, converting enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: General.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions**.)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

(J4-422A)

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1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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The Western Journal of Medicine

VOLUME 157 • NUMBER 4 • OCTOBER 1992

CONTENTS

ARTICLES

421 **Tuberculosis Chemoprophylaxis**

SHELLEY SALPETER, MD

From the Sonto Cloro Volley Medicol Center, Son Jose, Califarnia.

425 **The 10-Year Experience of an Academically Affiliated Occupational and Environmental Medicine Clinic**

LINDA ROSENSTOCK, MD, MPH; WILLIAM DANIELL, MD, MPH; SCOTT BARNHART, MD, MPH; BERT STOVER; JOSEPH CASTORINA, MD, MPH; SUSAN E. MASON, MSPH; NICHOLAS J. HEYER, MSPH, PhD; REBECCA HUBBARD; JOEL D. KAUFMAN, MD, MPH; CARL A. BRODKIN, MD, MPH; and MATTHEW KEIFER, MD, MPH

From the Occupatianal and Enviranmentol Medicine Progrom, University of Washingtan Schaals of Medicine and Public Health ond Community Medicine, Seottle.

430 **Controlling a Syphilis Epidemic**

DEBORAH A. COHEN, MD, MPH; RICHARD SCRIBNER, MD, MPH; and DAVID CORY

From the Deportments of Fomily Medicine ond Preventive Medicine, University of Southern Californio School of Medicine, Los Angeles. Dr Cohen is currently with the Department of Medicine, Section of HIV, Louisiana Stote University Medicol Center, New Orleons. Mr Cory is on independent consultont in public heolth.

433 **Predicting Risk for Medical Malpractice Claims Using Quality-of-Care Characteristics**

SARA C. CHARLES, MD; ROBERT D. GIBBONS, PhD; PAUL R. FRISCH, JD, CAE; CHARLENE E. PYSKOTY, MA, MPH; DONALD HEDEKER, PhD; and NAVNEET K. SINGHA

From the Deportment of Psychiotry, School of Medicine ond the School of Public Health, University of Illinais, Chicaga; and the Deportment of Medicol-Legal Affoirs, Oregon Medical Association, Portlond.

CONFERENCES AND REVIEWS

440 **Overwhelming Postsplenectomy Infection—Still a Problem**

MALCOLM L. BRIGDEN, MD, FRCPC

Fram the Island Medical Labaratarias, Victorio, British Columbia, Conoda.

444 **Gastrointestinal Complications of Nonsteroidal Anti-inflammatory Drugs**

RICHARD R. BABB, MD

Fram the Gastraenteralagy Division, Pala Alto Medical Clinic, Pala Alta, California.

EPITOMES—IMPORTANT ADVANCES IN OPHTHALMOLOGY

448 **Medical Treatment of Retinal Infections in Patients With AIDS**

GARY N. HOLLAND, MD

449 **Photorefractive Keratectomy**

PETER J. McDONNELL, MD

449 **Macular Surgery**

JEFFREY K. LUTTRULL, MD

450 **Laser Treatment of Diabetic Retinopathy**

PAUL E. TORNAMBE, MD

451 **Retinitis Pigmentosa—New Advances in Ophthalmic Genetics**

VINH TAN TRAN, MD, PhD

(Continued on Page 406)

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‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus*. New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol*. 1990;66:131-1S1. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol*. 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation*. 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology*. 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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(Continued from Page 404)

451 **Current Therapy for Disorders of the Optic Nerve**
ANTHONY C. ARNOLD, MD

452 **Graves' Ophthalmopathy**
DENISE F. DUDLEY, MD, and JAMES C. ORCUTT, MD, PhD

453 **Small-Incision Cataract Operation**
RICHARD H. KEATES, MD, and KEVIN H. MERKLEY, MD

ALERTS, NOTICES, AND CASE REPORTS

454 **Maternal Death Due to Rupture of a Low Transverse Cesarean Section Incision During Labor at Home**
VAL A. CATANZARITE, MD, PhD; ERIN FOSTER; PAM ROBINETTE, RN; LARRY M. COUSINS, MD; and JACK M. SCHNEIDER, MD
From the Department of Maternal Fetal Medicine, Sharp Memorial Hospital Women's Center, San Diego, California.

455 **Isolation of *Borrelia burgdorferi* From Ticks in Southern California**
HILDY B. MEYERS, MD, MPH; DOUGLAS F. MOORE, PhD; GEORGE GELLERT, MD, MPH, MPA; GARY L. EULER, DrPH; THOMAS J. PRENDERGAST, MD, MPH; MAHER BADRI, MD, MPH; JAMES P. WEBB, PhD; and CARRIE L. FOGARTY
From the Orange County Health Care Agency, Santa Ana; the Preventive Medical Services Division, Department of Public Health, San Bernardino County, San Bernardino; and the Orange County Vector Control District, Garden Grove, California.

COMMENTARY

457 **Personal Renewal**
JOHN W. GARDNER, PhD
From the Graduate School of Business, Stanford University, Stanford, California.

EDITORIALS

460 **'New Habits of Mind'—Bridging the Gap Between Public Health and Clinical Medicine**
ROSEMARY K. SOKAS, MD, MOH
Dr Sokas is Associate Professor of Medicine, Division of Occupational and Environmental Medicine, George Washington University Medical Center, Washington, DC.

461 **Complications of Asplenia and Hyposplenism—Persistent Uncertainties**
BARBARA STYRT, MD
Dr Styrt is Associate Professor of Medicine and Microbiology and Public Health, Michigan State University, East Lansing.

463 **Treatment Strategies in the Prevention of Tuberculosis**
THOMAS L. PETTY, MD
Dr Petty is Director of Academic and Research Affairs and Professor of Medicine, University of Colorado Health Sciences Center, Denver.

465 **Nonsteroidal Anti-inflammatory Drugs and Ulcers**
ANDREW H. SOLL, MD
Dr Soll is Chief of Gastroenterology, Wadsworth Veterans Affairs Medical Center; and Director, Integrated Training Program in Gastroenterology, and Professor of Medicine, University of California, Los Angeles, School of Medicine.

(Continued on Page 408)

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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(Continued from Page 406)

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469 'What Kind of Work Do You Do?'
JEAN SPENCER FELTON, MD

469 Cancer Screening in Women
PHYLLIS J. SENTER, MD
JUDITH M. E. WALSH, MD, MPH, Responds

470 Exaggerated Threat of Childhood Lead Poisoning in California—Epidemic by Edict
EDGAR J. SCHOEN, MD

471 Another Health Food Hazard—γ-Hydroxybutyrate-induced Seizures
BRUCE T. ADORNATO, MD, and VICTOR TSE, MD

471 Licensing of Tissue Banks in California
GEORGE W. RUTHERFORD, MD

471 Pulse Oximeter Versus Electrocardiogram
HARRY J. COZEN, MD
KEVIN K. TREMPER, PhD, MD, Responds

472 Discounting Our Future
HARRY Z. COREN, MD
THEODORE G. GANIATS, MD, Responds

472 Meta-analyses Revisited
BENJAMIN J. GEIMAN and ARNOLD L. SMITH, MD

LESSONS FROM THE PRACTICE

474 A Suitcase Full of Pills
RICHARD E. WALTMAN, MD
From the Allenmore Medical Center, Tacoma, Washington.

OTHER FEATURES

403 Instructions for Authors

410 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington

439 Poem

480 Subscription Information

481 Classified Advertising

492 Western State Medical Associations' Meetings

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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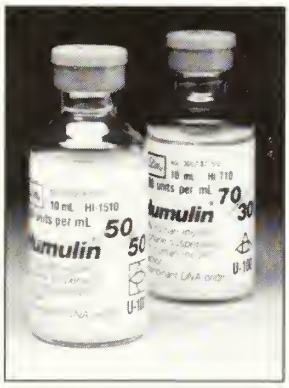

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ANESTHESIOLOGY

October 22-25—**American Pain Society: 11th Annual Meeting.** American Pain Society at San Diego. Thurs-Sun. Contact: APS, 5700 Old Orchard Rd, Skokie, IL 60077-1057. (708) 966-5595.

October 25-31—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Sheraton Kauai Resort, Poipu Beach, Kauai, Hawaii. Sun-Sat. 25 hrs. $395-$465. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 6-8—**Anesthesiology Update: 1992.** UCD at Monterey Plaza Hotel. Fri-Sun. 14 hrs. $350. Contact: UCD.

November 20-21—**Pain Management Conference.** UCD at Silverado Country Club. Fri-Sat. 12 hrs. $225. Contact: UCD.

January 6-9—**Anesthesia Update.** UCSD at Hotel del Coronado. Wed-Sat. Contact: UCSD.

January 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach, Maui, Hawaii. 1 wk. 21 hrs. $395. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

January 29-31—**31st Clinical Conference in Pediatric Anesthesiology.** Children's Hospitals Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 19-23—**67th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Diego Marriott Hotel & Marina, San Diego. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131-2553. (216) 642-1124.

March 26-28—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort, Dana Point. Fri-Sun. 9 hrs. $175-$245. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

CARDIOLOGY

October 17—**Current Advancements in Interdisciplinary Management of Third Stage Stroke.** American Geriatrics Society at Stroke Activity Center, Palm Springs. Sat. 7 hrs. Contact: Diane Hanner, PO Box 355, Palm Springs 92263. (619) 323-7676.

January 21-23—**Cardiology '93.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, Conference Manager, PO Box 2586, La Jolla 92038. (619) 459-1564.

March 11-13—**3rd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

DERMATOLOGY

October 17-18—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

January 15-17—**Practical Dermatology & Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. Contact: UCSD.

January 22-24—**Cutaneous Malignancies: 1993 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. $350. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

October 19-23—**Emergency Medicine Symposia I.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

October 26-30—**21st Annual Topics in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Mon-Fri. 32 hrs. $560. Contact: UCSF.

October 28-November 1—**Wound Management Workshop.** UCSD at San Diego Hilton Beach & Tennis Resort. Wed-Sun. Contact: UCSD.

October 29-November 1—**14th Year Biannual Wound Management Workshop.** UCSD at La Jolla Marriott. Thurs-Sun. 18 hrs. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

November 5-6—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Thurs-Fri. 15 hrs. $295-$495. Contact: Kathy Hester, (800) 451-7475.

November 9-13—**Emergency Medicine Symposia III.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

December 6-11—**Current Concepts in Emergency Care: 13th Annual Conference.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Jeannine Whidbee, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 7-11—**Emergency Medicine Symposia II.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

January 13-17—**The California Trauma Conference.** UCSD at Hotel del Coronado. Mon-Fri. 20 hrs. $400. Contact: UCSD.

January 18-22—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

January 23-30—**Wound Management.** UCSD at Royal Waikoloan, Kohala Coast, Island of Hawaii. 1 week. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-27—**Update: Controversies in Emergency & Primary Care.** American Institute of Postgraduate Education at Royal Lahaina Resort, Maui, Hawaii. 1 week. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

ENDOCRINOLOGY/METABOLISM

November 10-14—**VIIth International Symposium on the Biology of Vascular Cells.** Scripps Clinic and Research Foundation at Princess Resort Mission Bay, San Diego. Tues-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 19-20—**New Horizons in Diabetes Therapy.** Scripps Clinic and Research Foundation at Scripps Memorial Hospital, La Jolla. Fri-Sat. $175. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 10-11—**Advances in Endocrinology & Metabolism.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 12-13—**Diabetes Update.** UCSF at Ritz-Carlton Hotel, San Francisco. Fri-Sat. 11 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

October 15-18—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Maui Inter-Continental Hotel, Hawaii. Thurs-Sun. 16 hrs. $281-$375. Contact: UCLA Extension.

October 26-29—**Primary Care Update.** Interstate Postgraduate Medical Association of North America at Riviera Hotel & Casino, Las Vegas. Mon-Thurs. 24 hrs. $225-$325. Contact: IPMA, PO Box 5474, Madison, WI 53705. (608) 257-1401.

November 12-15—**CME/GOLF Meeting.** Nevada Academy of Family Physicians at Rio Hotel, Las Vegas. Thurs-Sun. 17 hrs. $225. Contact: Shone Ariotti, 895 Adams Blvd, Boulder City, NV 89005. (702) 293-0406.

February 12-14—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 418)

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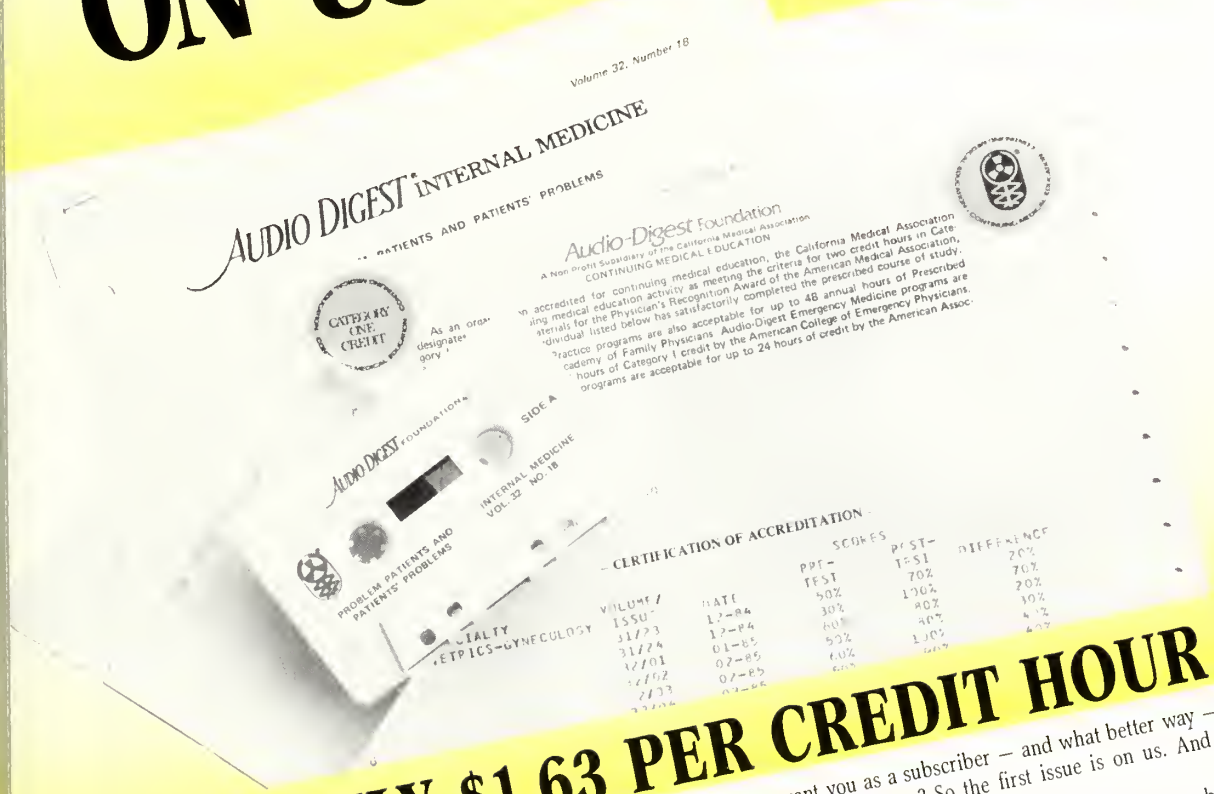

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PACE PROFILE

Vaughn A. Starnes, M.D. has joined the University of Southern California School of Medicine.

Vaughn A. Starnes, M.D., has joined the University Southern California School of Medicine as Professor Surgery, Chief of the Division of Cardiothoracic Surge and Director of the USC Cardiothoracic Center at US University Hospital, Childrens Hospital Los Angeles and L Angeles County+USC Medical Center. Dr. Starnes is a wor recognized leader and innovator in adult and pediatric hea heart-lung and lung transplantation and treatment of congeni heart disease.

In 1984 Dr. Starnes was accepted to the Stanford Cardiotho cic program, where he completed two years as a resident in card vascular surgery, and one year as chief resident in cardi transplantation under the guidance of Norman Shumway, M.D

In 1988 Dr. Starnes was appointed director of Stanford's hea lung transplantation program, and later became chief of pediat heart surgery and director of the transplant program at Stanfo Lucile Salter Packard Childrens Hospital. He performed about 4 adult and pediatric cardiac cases annually at Stanford. In additi to his adult cardiothoracic surgical expertise, Dr. Starnes earned national reputation for his work in pediatrics.

Dr. Starnes also pioneered lung and heart-lung transplant p cedures in children that previously had only been performed adults. In 1991 he was the first surgeon to transplant the l upper lobe of a 2-year-old donor into a newborn with pulmon hypertension who could not be weaned off ECMO (Extracorpor Membrane Oxygenation). In 1992, he performed the first lu transplant on a baby with congenital diaphragmatic hernia.

University of Southern Californ

USC Cardiothoracic Center

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mprehensive Services

e USC Cardiothoracic Center is one of andful of centers in the country to pro- e a comprehensive range of adult and diatric cardiovascular services includ- adult and pediatric heart, heart-lung d lung transplantation.

The Center features a non-invasive vas- ar diagnostic laboratory, diagnostic giography laboratory and state-of-the- cardiac catheterization laboratories. If icated, cardiac surgeons incorporate latest corrective surgical techniques conditions such as ventricular and al arrhythmias and aortic diseases that olve aneurysms and dissections.

The Center also specializes in the treat- nt of infants with congenital heart ects including hypoplastic left heart drome, aortic valve disease, and trans- ition of the great vessels.

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At the Center, cardiologists, cardiothoracic surgeons, vascular surgeons, anesthesiologists, radiologists, interventional radiologists and allied medical professionals pool their extensive knowledge and expertise to provide patients with the full range of diagnostic and treatment alternatives.

Goal-Directed Research

As a university-based program, the Center is actively engaged in research. Specialists identify clinical problems and then seek the answer in the laboratory. Patients benefit from this link between bench and bedside, which promises to provide a better understanding of the physiology of the disease process.

Community Resource

As a vital component of the USC School of Medicine, the USC Cardiothoracic Center serves as a key educational resource for community-based and referring physicians. Physicians are encouraged to contact the Center through PACE to obtain telephone consultations, and access information regarding new patient care techniques, medications and research protocols to receive assistance with patient management concerns.

A new era is unfolding at the USC School of Medicine. We invite you to be a part of it. For more information about the USC Cardiothoracic Center, or to refer a patient, dial:
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ABSTRACTS OCTOBER 1992

(Rosenstock L, Daniell W, Barnhart S, et al: The 10-year experience of an academically affiliated occupational and environmental medicine clinic. West J Med 1992 Oct; 157:425-429)

Occupational and environmental diseases are underrecognized. Among the barriers to the successful diagnosis, treatment, and prevention of these conditions are inadequate consultative and information resources. We describe the 10-year clinical and training experiences of an academically affiliated referral center that has as its primary goal the identification of work-related and other environmental diseases. The University of Washington Occupational and Environmental Medicine Program has evaluated 6,048 patients in its diagnostic and screening clinics. Among the 2,841 seen in the diagnostic clinics, 1,553 (55%) had a work-related condition. The most prevalent diagnoses included asbestos-related lung disease (n=603), toxic encephalopathy (n=160), asthma (n=119), other specific respiratory conditions (n=197), carpal tunnel syndrome (n=86), and dermatitis (n=82). The clinics serve as a training site for fellows in the specialty training program, primary care internal medicine residents, residents from other medical specialties, and students in industrial hygiene, toxicology, and occupational health nursing. The program serves two additional important functions: providing consultative services to community physicians and training specialists and other physicians in this underserved area of medicine.

WORK-RELATED DISEASE
ENVIRONMENTAL MEDICINE
OCCUPATIONAL MEDICINE TRAINING

(Rosenstock L, Daniell W, Barnhart S, et al: The 10-year experience of an academically affiliated occupational and environmental medicine clinic. West J Med 1992 Oct; 157:425-429)

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WORK-RELATED DISEASE
ENVIRONMENTAL MEDICINE
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WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

CARDIZEM® CD Product Information as of October 1991
CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Mattson RH, Prevey ML, et al. JAMA 1989;261(22):3273-3274

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17th Annual Internal Medicine Series
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The Hilton, Walt Disney World Village

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16th Annual Critical Care Medicine Conference
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(Continued from Page 410)

GERIATRICS

November 16-18—**Geriatrics Update—1992.** Sharp Memorial Hospital at Loew's Coronado Bay Resort. Mon-Wed. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 5-6—**Alzheimer's Disease New Advances in Treatment.** UCSD at San Diego. Fri-Sat. Contact: UCSD.

HEMATOLOGY

November 14—**Hyperlipidemia Update: 1992.** UCD at Cancer Center Auditorium, Sacramento. Sun. Contact: UCD.

December 4—**Current Issues in Hemophilia Care.** Orthopaedic Hospital Los Angeles at Hyatt Regency Alicante, Anaheim. Sat. 6 hrs. $100. Contact: Hemophilia Care, Meeting Management, 5665 Oberlin Dr, #110, San Diego 92121. (619) 453-6222.

February 14-17—**Clinical Hematology and Oncology: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sun-Wed. 18 hrs. $385. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

INFECTIOUS DISEASES

October 16-17—**7th Annual Kuzell Institute Symposia: Advances in Rheumatology and Progress Against Infectious Diseases.** California Pacific Medical Center at Sheraton Palace Hotel Grand Ballroom, San Francisco. Fri-Sat. 12 hrs. Contact: Kristy Davison, CPMC, 2340 Clay St, Rm 219, San Francisco 94115. (415) 923-3441.

October 21—**22nd Annual Respiratory/Infectious Diseases Symposium.** Enloe Hospital at Esplanade Building, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

November 13-15—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

December 14-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

February 4-6—**11th Annual Practical Update of Infectious Diseases.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. 12 hrs. $160. Contact: UCD.

INTERNAL MEDICINE

November 11—**19th Annual Gastroenterology Symposium.** Enloe Hospital at Esplanade Building, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

January 30-February 1—**Advanced Nephrology: Nepbrology for the Consultant.** UCSD at La Jolla Marriott. Sat-Mon. Contact: UCSD.

February 5-7—**State of the Art Urology.** UCLA at Ritz-Carlton, Marina del Rey. Fri-Sun. Contact: UCLA Extension.

February 20-25—**Topics and Advances in Internal Medicine.** UCSD at Hyatt Regency. Sun-Thurs. Contact: UCSD.

March 19-25—**Internal Medicine 1993: A Comprehensive Review.** Sharp Memorial Hospital at Hotel Del Coronado, San Diego. Fri-Tues. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

NEUROLOGY

October 23-24—**Transcranial Doppler and Cerebral Blood Flow Monitoring: Applications in Neurology, Neurosurgery and Anesthesiology.** UCLA at Sheraton Miramar Hotel, Santa Monica. Fri-Sat. Contact: UCLA Division of Neurosurgery, (310) 206-0626.

February 4-6—**16th Annual: Neurology for Non-Neurologists.** UCSD at Doubletree Hotel Horton Plaza, San Diego. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 11-13—**26th Annual Recent Advances in Neurology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 15 hrs. $345. Contact: UCSF.

OB/GYN

November 5-6—**Basic Colposcopy & Update in Colposcopy and Lower Genital Neoplasia.** University of Western Ontario Canada at Palm Springs Marquis. Thurs-Fri. Contact: Cecil Wright, 877 Richmond St, London, Ontario, Canada N6A 3J1. (519) 438-1411.

November 7—**Electrosurgery for Lower Genital Disease.** University of Western Ontario Canada at Palm Springs Marquis. Sat. Contact: Cecil Wright, 877 Richmond St, London, Ontario, Canada N6A 3J1. (519) 438-1411.

December 3-5—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas. Thurs-Sat. $250. Contact: Brenda Ram, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

January 17-19—**Annual Ambulatory Gynecology Update: 1993.** UCD at Incline Village, Nevada. Sun-Tues. Contact: UCD.

February 11-14—**48th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: C. James Dowden, OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 17-19—**Contemporary Obstetrical & Transvaginal Ultrasound.** UCSD. Wed-Fri. Contact: UCSD.

March 13—**Women's Health Issues.** UCD at Cancer Center Auditorium. Sat. Contact: UCD.

OCCUPATIONAL/ENVIRONMENTAL

October 15-18—**36th Annual Western Occupational Health Conference.** American College of Occupational and Environmental Medicine at Sheraton Harbor Island, San Diego. Thurs-Sun. 18 hrs. $250-$335. Contact: WOHC, 50 First St, Ste 300, San Francisco 94105-2411. (415) 764-4803.

October 19-30—**Occupational and Environmental Medicine: Session II.** UCSF at Miyako Hotel, San Francisco. 1½ wks. 80 hrs. $1,400. Contact: UCSF.

KEY TO ABBREVIATIONS

CMA — California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC — California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW — Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: — Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN — Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: — University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: — University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA — University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: — University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF — University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC — University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 419)

CONTINUING MEDICAL EDUCATION

(Continued from Page 418)

November 2-6—**Advances in Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

January 25-February 5—**Occupational & Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. 1½ weeks. 80 hrs. $1400. Contact: UCSF.

February 8-12—**Occupational & Environmental Medicine: Session III.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 24—**Melanoma and Pigmented Lesions.** Stanford University Medical Center at Fairchild Auditorium, Stanford. Sat. Contact: STAN.

October 26-28—**16th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Meeting Management, Cancer Symposium, 5665 Oberlin Dr, #110, San Diego 92121. (619) 453-6222.

November 5-8—**Prostate Cancer.** Sutter Health at Hyatt Regency, Sacramento. Thurs-Sun. Contact: Sutter Health, (916) 733-3883.

March 4-5—**Dimensions of Caring 1993: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Doubletree Hotel Horton Plaza, La Jolla. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-9592.

OPHTHALMOLOGY

December 10-12—**Ophthalmic Surgical Complications: OOPS—What Do I Do Now?** UCSF at Ritz-Carlton Hotel and UCSF Campus, San Francisco. Thurs-Sat. 12 hrs. $200-$375. Contact: UCSF.

ORTHOPEDICS

October 31—**Orthopedics Symposium.** Sutter Health at Sheraton Sunrise, Rancho Cordova. Sat. Contact: Sutter Health, (916) 733-3883.

November 5-6—**Low Back Pain and Its Relation to the Sacroiliac Joint.** UCSD at San Diego Convention Center. Thurs-Fri. 12 hrs. $335. Contact: UCSD.

November 19-21—**San Diego Spine Symposium.** UCSD at San Diego Marriott. Thurs-Sat. 11 hrs. Contact: UCSD.

December 3—**9th Annual Symposium on Common Musculoskeletal Problems: Current Concepts in Diagnosis and Management of Arthritis.** VA Medical Center Sepulveda. Thurs. 6 hrs. Contact: Arun Mehta, MD, VA Med Ctr, RMS 117, Sepulveda 91343-2036. (818) 895-9344.

December 9-13—**Fall Symposium on Back Pain.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

OTOLARYNGOLOGY

October-December 1992—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Mon-Sat. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

November 5-7—**Otolaryngology Update: 1992.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17 hrs. $395. Contact: UCSF.

PATHOLOGY

October 17—**32nd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Irvine Marriott. Sat. Contact: Sylvie Tarro, (310) 641-8152.

October 26-30—**Urological Pathology: Current Concepts and Recent Developments.** American Society of Clinical Pathologists at Santa Barbara. Mon-Fri. 25.5 hrs. $690. Contact: ASCP, 2100 W Harrison St, Chicago, IL 60612. (312) 738-1336.

PEDIATRICS

October 19-24—**Lactation Management Education Program.** UCSD at Wellstart, San Diego. Mon-Sat. Contact: UCSD.

(Continued on Page 476)

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TAGAMET*[1] *(brand of cimetidine)

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or PDR. The following is a brief summary.

Indications and Usage: *1) Short-term treatment of active duodenal ulcer, (2) maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer, (3) short-term treatment of active benign gastric ulcer, (4) erosive gastroesophageal reflux disease, (5) prevention of upper gastrointestinal bleeding in critically ill patients, (6) treatment of pathological hypersecretory conditions*

Contraindications: *Tagamet is contraindicated for patients known to have hypersensitivity to the product*

Precautions: *Rare instances of cardiac arrhythmias and hypotension have been reported following the rapid administration of Tagamet (cimetidine hydrochloride) Injection by intravenous bolus*

Symptomatic response to Tagamet therapy does not preclude the presence of a gastric malignancy There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy

Reversible confusional states have been observed on occasion, predominantly in severely ill patients

Tagamet has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole Clinically significant effects have been reported with the warfarin anticoagulants, therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when Tagamet is administered concomitantly Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects

However, a crossover study in healthy subjects receiving either Tagamet 300 mg q i d or 800 mg h s concomitantly with a 300 mg b i d dosage of theophylline (Theo-Dur®, Key Pharmaceuticals, Inc) demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h s regimen, particularly in subjects aged 54 years and older Data beyond ten days are not available (Note All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy)

In a 24-month toxicity study in rats, at dose levels approximately 8 to 48 times the recommended human dose, benign Leydig cell tumors were seen These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving Tagamet

A weak antiandrogenic effect has been demonstrated in animals In human studies, Tagamet has been shown to have no effect on spermatogenesis, sperm count, motility, morphology or in vitro fertilizing capacity

Pregnancy Category B Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Tagamet There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Lack of experience to date precludes recommending Tagamet for use in children under 16 unless anticipated benefits outweigh potential risks, generally, nursing should not be undertaken by patients taking the drug since cimetidine is secreted in human milk

Adverse Reactions: *Diarrhea, dizziness, somnolence, headache Reversible confusional states (e g , mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation), predominantly in severely ill patients, have been reported Reversible impotence in patients with pathological hypersecretory disorders receiving Tagamet, particularly in high doses for at least 12 months, has been reported The incidence of impotence in large-scale surveillance studies at regular doses has not exceeded that commonly reported in the general population Gynecomastia has been reported in patients treated for one month or longer Decreased white blood cell counts in Tagamet-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia Dose-related increases in serum transaminase have been reported Reversible adverse hepatic effects, cholestatic or mixed cholestatic-hepatocellular in nature, have been reported rarely Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely A single case of biopsy-proven periportal hepatic fibrosis in a patient receiving Tagamet has been reported Small, possibly dose-related increases in plasma creatinine have been reported Rare cases of fever, interstitial nephritis, urinary retention, pancreatitis and allergic reactions, including anaphylaxis and hypersensitivity vasculitis, have been reported Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists Reversible arthralgia, myalgia and exacerbation of joint symptoms in patients with preexisting arthritis have been reported rarely Rare cases of polymyositis have been reported, but no causal relationship has been established Mild rash and, very rarely, cases of severe generalized skin reactions (e g , Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma) have been reported with H_2-receptor antagonists Reversible alopecia has been reported very rarely*

How Supplied: Tablets: *200 mg tablets in bottles of 100, 300 mg tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only), 400 mg tablets in bottles of 60 and Single Unit Packages of 100 (intended for institutional use only), and 800 mg Tiltab® tablets in bottles of 30 and Single Unit Packages of 100 (intended for institutional use only)*

Liquid: *300 mg/5 mL, in 8 fl oz (237 mL) amber glass bottles and in single-dose units (300 mg/5 mL), in packages of 10 (intended for institutional use only)*

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Vials: *300 mg/2 mL in single-dose vials, in packages of 25, and in 8 mL multi-dose vials, in packages of 10 and 25*

Single-Dose Premixed Plastic Containers: *300 mg in 50 mL of 0 9% Sodium Chloride in single-dose plastic containers, in packages of 4 units No preservative has been added*

Exposure of the premixed product to excessive heat should be avoided It is recommended the product be stored at controlled room temperature Brief exposure up to 40°C does not adversely affect the premixed product

ADD-Vantage® Vials: *300 mg/2 mL in single-dose ADD-Vantage® Vials, in packages of 25*

Tagamet (cimetidine hydrochloride) Injection premixed in single-dose plastic containers is manufactured for SmithKline Beecham Pharmaceuticals by Baxter Healthcare Corporation, Deerfield, IL 60015

BRS-TG L87

1. Data from randomized, controlled studies On file, SmithKline Beecham Pharmaceuticals.

2. Palmer RH, Frank WO, Rockhold FW, et al Cimetidine 800 mg twice daily for healing erosions and ulcers in gastroesophageal reflux disease. *J Clin Gastroenterol* 1990;12(suppl 2) S29-S34

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brand of cimetidine

Before prescribing, please see brief summary of prescribing information on adjacent page.

Articles

Tuberculosis Chemoprophylaxis

SHELLEY SALPETER, MD, *San Jose, California*

The incidence of tuberculosis in the United States, after decreasing for many years, has recently begun to climb at an alarming rate. This rise is due mainly to excess cases in high-risk groups including human immunodeficiency virus-infected patients, the elderly, the foreign born, and the homeless. In the United States tuberculosis has been associated with a 10% mortality despite adequate treatment.

The tuberculin skin test is a safe and inexpensive test for detecting tuberculous infection. To improve its predictive value the diagnostic criteria for classifying a positive reaction have recently been revised. High-risk populations should be screened to identify those persons who would most benefit from preventive treatment. Isoniazid therapy taken for 6 to 12 months is a safe and highly effective means of preventing tuberculous infection from developing into active disease. The most worrisome toxicity of isoniazid, fatal hepatitis, is extremely rare; when patients are monitored closely the incidence of death from hepatotoxicity is less than 0.01%.

(Salpeter S: Tuberculosis chemoprophylaxis. West J Med 1992 Oct; 157:421-424)

A successful preventive treatment strategy against a disease must meet certain requirements. There must be a clearly identifiable population at risk in whom screening efforts can be concentrated and preventive treatment targeted. There should be a good screening test with high predictive value that is safe and inexpensive. Finally, there must be an effective preventive treatment where the benefits far outweigh the risks. I will discuss an effective preventive treatment strategy against tuberculosis that if followed could substantially curtail the spread of the disease.*

Epidemiology of Tuberculosis in the United States

The incidence of active tuberculosis (TB) in the United States is about 10 cases per 100,000 per year.[1,2] More than 10 million people, or 5% of the population, have asymptomatic infections.[1] A person with a recent infection is at much higher risk for activation within the first year (5%) compared with someone with a remote infection (0.2% per year).[1,3] More than 90% of the total cases each year, however, are from the large pool of remote infections.[1]

Tuberculosis has been associated with a 10% mortality, occurring mainly in persons 65 years or older.[4,5] In more than half the cases the diagnosis is made after death.[6] Causes of death include pneumonia, hemorrhage, intestinal perforation, and meningitis.

The incidence of TB had been gradually declining in the United States for 40 years, but since 1985 it has been steadily climbing.[2] This rise is due in large part to the increasing number of cases in persons with the human immunodeficiency virus (HIV).[2,7] A prospective study done at a methadone-maintenance center showed that TB developed in HIV-infected persons with positive tuberculin skin tests at a rate of 8% per year.[8] The cumulative incidence of TB in HIV-infected patients is 2% per year, for a relative risk of 100 to 500 times average.[3,7,8]

Tuberculosis in HIV-infected patients tends to present atypically, with extrapulmonary or disseminated disease.[9] Active pulmonary disease is also atypical, often presenting with infiltrates in all lung fields or with mediastinal and hilar adenopathy. Tuberculosis in HIV-infected patients usually occurs early in the course of the disease, before or concurrent with the development of the acquired immunodeficiency syndrome (AIDS).[8,10] The Centers for Disease Control recently revised the case definition of AIDS to include extrapulmonary TB in HIV-infected patients.[11] All persons with TB or tuberculous infection should be tested for HIV because the management of seropositive patients is different from that for the general population.[9]

Many other groups are at high risk for TB developing.[12,13] The prevalence of asymptomatic infections approaches 50% in immigrants from Asian and Latin American countries, some elderly nursing home patients, the homeless, and underserved minorities.[3,14-17] Groups at high risk for activating latent infection include close contacts of patients with active pulmonary TB, those whose skin tests recently converted from negative to positive, persons with abnormal chest radiographs consistent with old TB, persons with alcoholism, and drug injecters.[12] Medical conditions that increase the risk of activation are immunosuppression (including corticosteroid use), silicosis, end-stage renal disease, diabetes mellitus, malnutrition or notable weight loss, and certain malignant neoplasms, including leukemia, lymphoma, and carcinomas of the upper gastrointestinal tract.[12] Clinical studies have not yet clarified the specific relative risks these conditions carry, but empiric evidence indicates that there may be at least a fourfold risk for activation.[4,13]

Tuberculosis Screening

The best test currently available to detect TB infection is the skin test using purified-protein derivative tuberculin. An intermediate-strength test containing 5 tuberculin units (TU) is administered intradermally to cause a delayed hypersensitivity reaction.[18] Strengths other than 5 TU should not be used because their biologic activities have not been quanti-

*See also "Treatment Strategies in the Prevention of Tuberculosis," by Thomas L. Petty, MD, on pages 463-465 of this issue.

From the Santa Clara Valley Medical Center, San Jose, California.
Reprint requests to Shelley Salpeter, MD, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
TB = tuberculosis

fied.[18] After the tuberculin is administered, the amount of induration is determined at 48 to 72 hours, but it usually remains positive for as long as a week.[15] If the reaction is negative, the test should be repeated. A positive reaction indicates a recall of immunity that may have waned over the years. This booster phenomenon is most common in persons aged 55 or older and can be seen from a week to a year after a previously negative test.[18-20] Persons who are screened on a yearly basis should receive this two-step testing to minimize confusion between a boosted reaction and a true conversion because treatment options differ for these two groups.[18,20] In addition, testing should be repeated in anyone who may have decreased immune responsiveness. This includes older persons and those with HIV infection or concomitant illness. Controls are often used to test for anergy, which is common in ill patients.[18]

To maximize the predictive value of the tuberculin skin test, the diagnostic criteria for a positive reaction have recently been revised.[18] A reaction of 5 mm or greater is considered positive for close contacts of infectious patients, persons with known or suspected HIV infection, and persons with a clinical suspicion of tuberculous infection or disease (characterized by an abnormal chest radiograph or symptoms). This low cutoff maximizes sensitivity while maintaining a fairly high specificity. A reaction of 10 mm or more is considered positive for persons from any other high-risk or high-prevalence group.[18] This broad category includes health care workers and even the general population of California (R. Saw, MD, State TB Control Program, written communication, July 1990).[18] In most of the United States where the prevalence of TB is low, the cutoff is increased to 15 mm for persons without any risk factor.[18]

It is important to remember that all patients with a positive tuberculin skin test must have active disease ruled out.[13] This is usually accomplished with a chest x-ray film, and if that is abnormal, then sputum specimens are obtained for acid-fast stains and culture. Extrapulmonary manifestations of TB have been increasing in frequency, especially in patients with HIV infection, and should be considered in the workup. If active disease is suspected, it is important to start antituberculous treatment while awaiting culture results.[13] It is often difficult to differentiate active from inactive disease on chest radiographs, and in those cases comparison with old films can be helpful. Stable chest films for at least four months provide good evidence for inactive disease.[18]

Chest radiographs consistent with old TB usually show fibrotic changes in the apices and pleura.[18] The amount of scarring seen appears to be proportional to the bacillary load and the risk for activation, which may be as high as 5% per year.[13,21] Those with substantial fibrosis on chest films require longer courses of isoniazid, which will be outlined later. Solitary calcified granulomas are thought to carry no increased risk for activation.[21]

Recommendations for Screening

There is no consensus on recommendations for who should be screened and how often. It is clear that screening efforts should be concentrated on high-risk groups and those people in contact with high-risk groups, such as health care professionals.[12,18] The test could be repeated on a yearly basis or even more often for some high-risk groups.[12,22] To reach many high-risk persons who have minimal contact with the health care system, skin testing programs should be set up at facilities such as shelters for the homeless, immigration offices, welfare departments, prisons, and long-term care facilities.[12,14,22] In addition, every adult in the United States should probably be screened at least once.[22]

Persons with previous bacille Calmette-Guérin vaccination have a gradual waning of tuberculin responsiveness over time. They should be screened and treated as if they were never vaccinated.[18] The vaccine, derived from a strain of *Mycobacterium bovis*, has been available for many years, but studies have shown that it offers minimal to no protection against the development of TB, and its use has been largely abandoned in adults.[13]

Isoniazid Chemoprophylaxis

Chemoprophylaxis with 300 mg of isoniazid—10 mg per kg for children—given daily for 6 to 12 months has been used to decrease the risk of active TB developing.[13] The efficacy of chemoprophylaxis ranges from 65% to 98%, depending on the length of treatment and level of compliance.[4,21,23-25] Protection lasts for at least 20 years and presumably for life.[13] In healthy patients with normal or minimal chest film findings, a 6-month course of treatment is as effective as a 12-month course and is more cost-effective.[21,23,25] The efficacy of prophylaxis in HIV-infected patients has not yet been documented, but the good response to standard chemotherapy for active disease suggests that a 12-month course of isoniazid should be effective as preventive therapy.[9,10]

Risks of Isoniazid Therapy

Transient asymptomatic elevations of aminotransferase levels occur in 10% to 20% of patients and carry no increased risk for hepatitis.[13] The risk for clinical hepatitis in young healthy adults is 0.3%, but this can increase to as much as 2.6% for those with daily alcohol use, chronic liver disease, and advanced age.[26]

Fatal hepatotoxicity is much rarer than previously estimated. A survey from 1972 showed 8 deaths in almost 14,000 patients treated with isoniazid.[26] All of the deaths were in patients older than 35, and most were in patients with severe alcoholism who were not receiving routine monitoring for liver function abnormalities.[26,27] There have subsequently been several prospective clinical trials and epidemiologic surveys that observed more than 14,000 patients on isoniazid therapy with improved monitoring guidelines, and no fatal hepatotoxicity has been found.[24,28-38] Peripheral neuropathy occurs rarely with isoniazid therapy and is preventable with 10 to 25 mg of pyridoxine hydrochloride a day.[39] Vitamin B_6 should be added only for patients at higher risk for neuropathy developing.[13] Risk factors include age older than 65, pregnancy, diabetes mellitus, chronic renal failure, alcoholism, treatment with anticonvulsants, and malnutrition.

Another side effect from isoniazid therapy is a vague impairment of concentration, which may be avoided by administering the dose at night.[39] Gastrointestinal symptoms, dizziness, acne, and allergic rashes have also been reported.[28,29]

Special Precautions With Isoniazid Use

There are a few absolute contraindications for isoniazid treatment.[13] The medicine should not be given to someone who has previously had a severe isoniazid hepatitis or a hypersensitivity reaction (like fever, rash, or arthritis). Isoniazid treatment should also be avoided in patients with acute liver disease.

Pregnancy is not an absolute contraindication for isoniazid therapy. No teratogenicity has been documented with its use, and it has been used in pregnant women with active TB, even in the first trimester.[13] A recent study, however, reported fatal isoniazid hepatitis in two young women shortly after delivery.[40] No prospective trials or surveys have been published to assess the risk in pregnant and postpartum women, but it is reasonable to withhold preventive therapy until after delivery, unless there is a high risk of TB activation. In those patients, treatment could begin after the first trimester with close patient monitoring.[13]

The concurrent use of phenytoin with isoniazid may be associated with increased serum concentrations of both drugs. Phenytoin levels should be monitored and the dose adjusted as needed.[13] Similarly, isoniazid interferes with the metabolism of disulfiram, carbamazepine, anticoagulants, benzodiazepines, and vitamin D, often requiring a reduction in the dose of these drugs.[39] The dose of isoniazid in these cases should remain the same.

Patient Management on Isoniazid Therapy

It is recommended that all patients be monitored on a monthly basis for symptom review and to evaluate compliance.[13] This can be done in person or by telephone. If there are any symptoms that could indicate hepatic toxicity, therapy should be withheld pending the results of liver function tests. No more than 30 pills should be dispensed at one time. In addition to close monitoring of symptoms, patients at increased risk for hepatic toxicity, including all those older than 35, should get baseline and periodic liver function tests, possibly every two to three months. Isoniazid should be stopped if the aspartate aminotransferase level exceeds three to five times the upper limit of normal.[13]

Recommendations for Isoniazid Chemoprophylaxis

The current recommendations for who should receive isoniazid chemoprophylaxis are listed in Table 1.[13,41] The list includes all persons with a reaction of at least 5 mm who have known or suspected HIV infection, are close contacts of patients with infectious TB, or have fibrotic changes on chest radiographs after active TB has been ruled out. Persons in these categories who have negative skin tests associated with anergy should also receive chemoprophylaxis in certain situations. Anergic patients with HIV infection should be treated if they are close contacts of infectious cases or if there is a past history of a positive skin test.[13,42] In addition, chemoprophylaxis should be considered for anergic HIV-infected persons who come from a group in which the prevalence of TB infection is at least 10%.[42] This includes drug injecters, prisoners, residents of long-term care facilities, immigrants, the homeless, and underserved minorities. Close contacts younger than 18 years should be treated until the skin test is repeated at three months.[13] Note that it is recommended that patients with HIV infection or notable abnormalities on chest radiographs be treated for 12 months with isoniazid and all other patients should receive it for 6 months.[13,21,41]

The management of low-risk tuberculin reactors is controversial. The recommendation to withhold chemoprophylaxis for low-risk reactors older than 35 came as a result of the 1972 survey and has not been revised since, even though the risk of death in monitored patients appears to be negligible.[43] Some studies using decision analysis indicate that, even if there were a significant mortality, all persons with a positive reaction of an unknown duration would benefit from chemoprophylaxis regardless of age.[5,23] The benefit is even greater when considering the spread to others. It is estimated that each case of infectious TB ultimately gives rise to another case.[27] In certain situations, such as nursing homes, shelters for the homeless, or communal houses for AIDS patients, the risk for spread is substantially higher, and epidemics have been reported.[7,14,16,44] Preventive treatment should be considered for those reactors who pose the greatest threat for transmission, such as residents of long-term care facilities and health care professionals in contact with susceptible persons.[3,27,41] It is important to involve the patient in the decision-making process whenever possible. The risks and benefits of the treatment options could be outlined and the patient's preference elicited.

TABLE 1.—*Recommendations for Isoniazid Chemoprophylaxis*

Purified-Protein Derivative Induration	*Duration of Therapy, mo*
≥5 mm	
All persons with known or suspected HIV	12
All close contacts of those with infectious TB	6
All persons with abnormal chest radiographs (inactive)	12
≥10 mm	
All persons with recent tuberculin skin test conversion	6
All drug injecters (without HIV)	6
All persons with conditions that increase risk	6
≥10–15 mm	
Persons younger than 35	6

HIV = human immunodeficiency virus, TB = tuberculosis

Possible Alternatives to Chemoprophylaxis

Although no other drugs have clearly documented efficacy for prophylaxis, there are many situations in which alternative forms of treatment should be considered.[22] Rifampin, alone or in combination with other drugs, can be used for contacts of patients with known isoniazid-resistant TB, immigrants at high risk for isoniazid-resistant disease developing, or persons intolerant to isoniazid.[13,41,45] Preliminary data from experimental studies and ongoing clinical trials indicate that combinations of drugs given daily for two to three months have efficacies equal to a six-month course of isoniazid without increased toxicity.[36,46-48] Data from studies of patients with smear- and culture-negative pulmonary tuberculosis indicate that for reactors with substantial chest film findings, a four- to six-month course of two drugs may be equivalent to 12 months of isoniazid therapy.[32,33]

Soon we will probably be using short-course regimens as standard prophylaxis. The combinations of drugs may help combat the recent emergence of multiple-drug resistance.[49] Better compliance will be another advantage of this approach. If the toxicity turns out to be low, preventive treatment could be extended to include stable reactors of all ages and possibly eradicate the disease.

Discussion

Why, if we have an effective preventive treatment strategy, are we failing to control tuberculosis? To help answer that question, a retrospective study of 275 patients with active TB was done to evaluate if the disease could have been prevented.[50] A third of the patients had been out of the health care system for at least five years before TB developed, and they had not received screening. Another third had been seen by a health professional but were never screened. Of the third who had been screened, more than half had a positive skin test, but two thirds of the reactors (13% of the total cases) were not offered therapy. Less than 25% of the cases resulted from a failure in our present preventive treatment system, such as a lack of tuberculin sensitivity or isoniazid efficacy. The results of this study clearly indicate that better attention to the guidelines for screening and prophylaxis could have a substantial effect on the control of tuberculosis.

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Articles

The 10-Year Experience of an Academically Affiliated Occupational and Environmental Medicine Clinic

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Occupational and environmental diseases are underrecognized. Among the barriers to the successful diagnosis, treatment, and prevention of these conditions are inadequate consultative and information resources. We describe the 10-year clinical and training experiences of an academically affiliated referral center that has as its primary goal the identification of work-related and other environmental diseases. The University of Washington Occupational and Environmental Medicine Program has evaluated 6,048 patients in its diagnostic and screening clinics. Among the 2,841 seen in the diagnostic clinics, 1,553 (55%) had a work-related condition. The most prevalent diagnoses included asbestos-related lung disease (n=603), toxic encephalopathy (n=160), asthma (n=119), other specific respiratory conditions (n=197), carpal tunnel syndrome (n=86), and dermatitis (n=82). The clinics serve as a training site for fellows in the specialty training program, primary care internal medicine residents, residents from other medical specialties, and students in industrial hygiene, toxicology, and occupational health nursing. The program serves two additional important functions: providing consultative services to community physicians and training specialists and other physicians in this underserved area of medicine.

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Occupational diseases pose a considerable health burden to current and former workers in the United States,[1-4] but occupational health services have historically been isolated from the mainstream of medical education and clinical practice.[5] It is only in the past decade that a clinical specialty in occupational medicine has gained even a limited presence in American medical schools and teaching hospitals.[6-9] From just a handful in the early 1980s, there are now about 40 hospital-based, academically affiliated occupational medicine clinics in the United States. These clinics are involved in providing services aimed at the diagnosis, treatment, and prevention of work-related diseases. More recently several of these clinics have expanded their activities to include the evaluation of nonoccupational environmental exposures and conditions.

We describe here the clinical and training experiences of the first ten years of the University of Washington (Seattle) Occupational Medicine Clinic. The clinic was founded in July 1981 at Harborview Medical Center and focused on serving the Pacific Northwest. Goals defined at the outset were to assess the work-relatedness of disease, to train clinicians, and to screen for disease in selected worker populations.

Methods

The Occupational Medicine Clinic is based at Harborview Medical Center, one of the two University of Washington Health Sciences Center hospitals. The clinic is part of the Occupational and Environmental Medicine Program. Patients are referred by a variety of sources and screened to meet appointment criteria, which have varied over time. Before 1990, patients with possible nonoccupational environmental exposures or conditions were largely excluded from evaluation. Because of increasing demand for consultations about nonwork exposures, this exclusion criterion was eliminated. Beginning in 1989, when an occupational musculoskeletal clinic was started, patients with back pain who had previously been excluded from evaluation were seen routinely. Other exclusion criteria that persist to the present are patients who seek evaluation of Agent Orange exposures and those who identify workplace stress as the primary concern.

From the beginning, patient records have been maintained and housed in the Occupational and Environmental Medicine Program offices, separate from hospital records. A computerized patient data base has been in existence since the clinic began operation; this data base has evolved over time to optimize patient management functions and research needs. In addition to routine demographic data, the following coded information has been available for each patient throughout the ten-year period from July 1981 to July 1991:

- Referral source;
- Occupation and industry (3-digit codes from the Classified Index of Industries and Occupations, developed by the Bureau of Census and based on the Standard Industrial Classification and the Standard Occupational Classification systems) and employer name (coded only for those employed by 102 selected regional and local employers);
- Exposures: one or two possibly hazardous exposures per person in current or past employment, using a predetermined list of about 70 exposures grouped in nine categories—fumes, dusts, metals, solvents, pesticides, miscellaneous

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chemicals, physical factors, ergonomic factors, and other factors; and

- Work-related diagnoses: one or two diagnoses for possible and diagnosed occupational diseases, using a slightly modified version of the *International Classification of Diseases, 9th Revision.*

Each diagnosis is linked to one specific exposure (using the exposure list described) and to a determination of the likelihood of work-relatedness of the condition (none, possible, probable, definite). Conditions thought readily attributable to nonoccupational causes were generally not coded.

The coding of patient information from the diagnostic clinics was done by attending physicians only (to increase inter-rater reliability) with assistance by the clinic industrial hygienist for general exposure codes (including N.J.H.). Seven physicians (including L.R., W.D., S.B., J.C., and J.D.K.) have served as attending physicians in the clinic during the period covered. Coding forms are regularly entered into the clinic's microcomputer, and the data base is maintained and quality controls assured by the clinic's research scientist (currently B.S.).

Results

Demographic Characteristics

The Occupational and Environmental Medicine Program maintains two primary clinical activities: diagnostic clinics, including a general diagnostic clinic that was started in 1981 and a musculoskeletal clinic started in 1989, and screening clinics—arranged by contractual agreements to serve defined populations of workers—started in 1983. Overall, in the ten years of clinic operation, 6,048 persons have been evaluated; 2,841 have been evaluated in the diagnostic clinics and 3,207 in 1 of 18 screening programs arranged for a wide range of occupational groups, including workers with exposure to asbestos, firefighters, and hazardous waste workers (see Table 1).

TABLE 1.—*Occupational Cohorts Evaluated in Occupational and Environmental Screening Clinics (n=3,207)*

Workers	Persons Evaluated No.	(%)
Asbestos-exposed		
Plumbers and pipe fitters	777	(24)
Ship scalers	83	(3)
Sheet metal workers	402	(12)
Elevator workers	66	(2)
Shipyard painters	61	(2)
Others	20	(1)
Firefighters		
Seattle, Wash.	796	(25)
Other	73	(2)
Hazardous waste workers	467	(15)
Others	462	(14)

The demographic characteristics of patients evaluated in the diagnostic clinics are shown in Table 2. The clinic population is largely men of working age. The racial distribution of the clinic population is roughly comparable to that of the metropolitan area in which it is located. Physicians are the single largest of the varied referral sources. The program's screening clinics generate a sizable number (n = 196, 7%) of diagnostic clinic evaluations. Figure 1 shows the location of the residence of patients evaluated, with 56% (n = 1,518) of all patients at the time of evaluation residing in Seattle and King County, an additional 40% (n = 1,081) from elsewhere in Washington State, and 4% from out of state.

TABLE 2.—*Characteristics of Patients Seen in Diagnostic Occupational Medicine Clinics (n=2,841)*

Characteristic	Patients No.	(%)
Sex*		
Men	2,175	(76)
Women	652	(23)
Age, years		
Range	18-87	
Mean (±SD)	49	(±14)
Race		
White	2,177	(77)
African American	334	(12)
Other	164	(6)
Unstated	166	(6)
Referral source		
Physician	734	(26)
Self-referred	722	(25)
Legal	359	(13)
Union	286	(10)
Workers' compensation	148	(5)
Screening clinic	196	(7)
Employer	51	(2)
Other/unknown	345	(12)

*Information not available for 14 persons.

TABLE 3.—*10 Leading Work-Related Conditions Identified in the Diagnostic Occupational Medicine Clinics**

Condition	Patients No.	(%)
Asbestosis	389	(21)
Asbestos-related pleural disease	214	(12)
Specified respiratory conditions (excluding asthma and asbestos-related)	197	(11)
Acute or chronic encephalopathy	160	(9)
Specified musculoskeletal (excluding carpal tunnel syndrome)	142	(8)
Hearing loss	125	(7)
Asthma	119	(6)
Carpal tunnel syndrome	86	(5)
Dermatitis	82	(4)
Other specified intoxication	26	(1)
Total	1,540	(84)

*In all, 1,824 conditions were noted in 1,553 patients; only diagnoses deemed "probably" or "definitely" related to work are included.

Job Characteristics and Work-Related Diagnosis

Among the 2,841 patients evaluated in the diagnostic clinics, 1,553 (55%) were identified as probably or definitely having a work-related condition. The age and sex distribution of those with a work-related diagnosis is similar to those of the overall population (mean age, 50 ± 15, and 78% men). Referral sources of those diagnosed with an occupational disease are, however, somewhat different from those of the overall diagnostic clinic population; they are less likely to be

referred by a physician (15% versus 26%) and more likely to be referred by their union (32% versus 10%).

The ten leading work-related diagnoses are shown in Table 3. These ten categories account for 84% of all work-related diagnoses. Asbestos-related conditions are the most prevalent and reflect in part follow-up of screening activities focused on high-risk workers, with 121 (20%) of those found to have an asbestos-related disease referred from this source. The geographic distribution of the residence of patients with an asbestos-related condition is shown in Figure 2.

Secular trends in work-related diagnoses are displayed in Figure 3. The peak of new asbestos-related diagnoses in 1986 followed a large screening effort. The number of cases of carpal tunnel syndrome increased considerably after the opening of a clinic activity dedicated to musculoskeletal disorders. The number of asthma diagnoses has remained relatively constant over time.

Several medical conditions attributable to workplace factors were diagnosed infrequently, including toxic hepatitis (n = 7), vibration-induced peripheral vascular disease (n = 6), hard-metal lung disease (n = 4), urticaria (n = 3), lymphohematopoietic cancer (n = 3), chemical conjunctivitis (n = 5), myopathy or rhabdomyolysis (n = 3), and glomerulonephritis (n = 2). In all, 26 cases of multiple chemical sensitivity syndrome could be identified through the data base, of which 16 (62%) were thought to be probably work-related. This underrepresents the total number of patients diagnosed with this disorder and is likely due to physician discretion to code only those conditions deemed probably related to work.

In addition to characterizing clinic patients by diagnosis, all patients were assigned up to two types of possibly hazardous exposure on the job(s) of concern—either the current or most recent job or the one related to the problem under evaluation. The ten leading workplace exposures are shown in Table 4. Diagnostic clinic patients were employed in a wide variety of occupations and industrial settings, as shown in Tables 5 and 6.

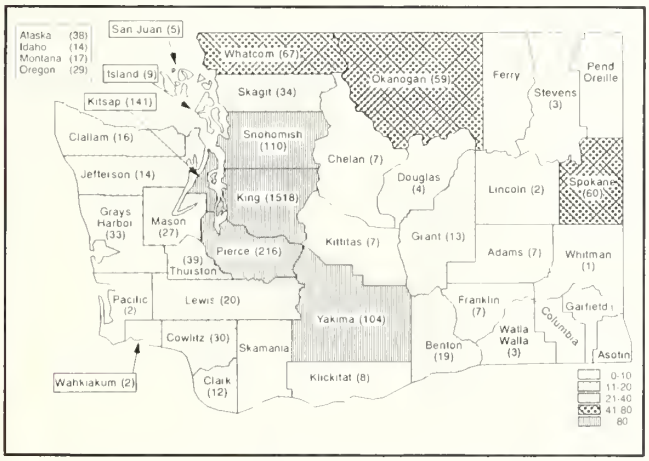

Figure 1.—The distribution of patients evaluated in the occupational medicine diagnostic clinics is shown by county in Washington State (n = 2,599) and those from Alaska, Idaho, Montana, and Oregon (n = 98). Not shown are 144 patients from other states or with unknown county of residence.

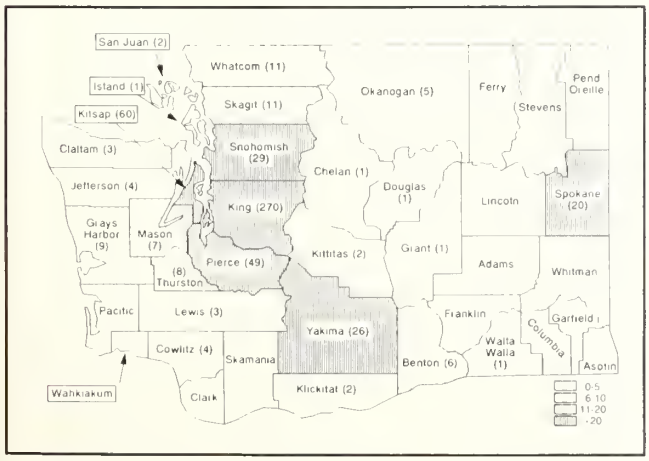

Figure 2.—The geographic distribution of the residence of patients diagnosed with an asbestos-related condition is shown. Not included are 67 patients not from Washington State or with unknown county of residence.

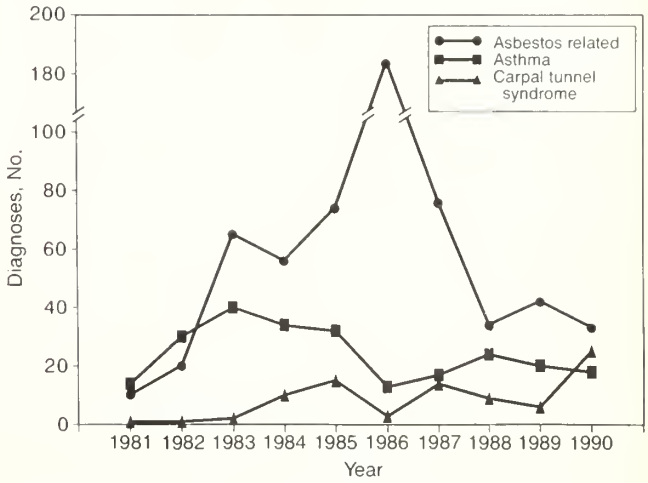

Figure 3.—The graph depicts time trends for the diagnosis of selected occupational diseases.

Training

The occupational medicine clinic is the major site for clinical training in occupational and environmental medicine at the University of Washington. Since 1987 specialty training in occupational medicine has been offered as a joint effort by the School of Medicine and School of Public Health and Community Medicine. At any one time about six fellows participate in the two-year training program. The program seeks to train physicians who have completed residency training in a primary care specialty (usually internal medicine) and are interested in academic or related careers. All fellows participate regularly in diagnostic clinic activities and to a limited extent in the screening clinic. Joint specialty training with the pulmonary disease and critical care medicine program has become formalized, and occupational and environmental medicine is an identified special emphasis area for the University of Washington Robert Wood Johnson Clinical Scholars Program.

In addition to training specialists in the field, the Occupational Medicine Clinic is a required rotation for all Seattle-based primary care internal medicine residents at the University of Washington. Other physicians in training (mostly internal medicine and family practice residents) elect on a regular basis to spend one or more months in the diagnostic clinic. About one to two medical students per year—from the University of Washington or elsewhere—do an

elective with the program combining clinical and research experiences.

Nonphysician training is also integrated into clinical activities. On an elective basis each year, several students in industrial hygiene, toxicology, occupational health nursing, and nurse practitioner programs have worked side by side with clinic staff—which, in addition to physicians, includes a full-time industrial hygienist and nurse practitioner.

Clinical teaching is predominantly patient-based in the ambulatory setting. An inpatient consultation service augments clinical experiences for fellows. In addition, a weekly clinic conference, which is open to all interested persons, is a regular forum for multidisciplinary discussion about the medical, legal, and social aspects of all cases evaluated in the diagnostic clinics. On a monthly basis, the conference is organized to include faculty and students in the graduate programs of industrial hygiene and occupational health nursing.

TABLE 4.—*Leading Potentially Hazardous Exposures Identified Among Diagnostic Clinic Patients*

Hazardous Exposure	Patients* No.	(%)
Asbestos	1,069	(38)
Solvents	588	(21)
Welding fumes	364	(13)
Vibration	260	(9)
Other chemicals	195	(7)
Metals, excluding welding and lead	95	(3)
Pesticides	74	(3)
Repetitive motion	54	(2)
Lead	53	(2)

*Each of 2,841 patients can be assigned up to 2 exposures.

TABLE 5.—*Most Common Occupations of Patients in the Diagnostic Occupational Medicine Clinic*

Occupation	Patients No.	(%)
Plumber, welder	251	(9)
Hazardous waste worker	144	(5)
Painter	128	(4)
Sheet metal, furnace installer	122	(4)
Laborer, sandblaster	94	(3)
Precision metal worker	93	(3)
Insulator, asbestos worker	80	(3)
Accountant, clerk	82	(3)
Sales	68	(2)
Machinist	62	(2)
Boilermaker	60	(2)
Janitor	47	(2)
Truck, bus driver	45	(2)
Carpenter	40	(1)
Electrician, technician	37	(1)
Pot operator	33	(1)
Machine operators	31	(1)
Auto mechanic	26	(1)
Ship fitter	26	(1)
Fabricators, assemblers	26	(1)
Total	1,495	(51)

TABLE 6.—*Most Common Industries Employing Patients of the Diagnostic Occupational Medicine Clinic*

Industry	Patients No.	(%)
Shipbuilding	555	(19)
Construction	485	(17)
Airplane manufacturing	130	(5)
Grocery store	81	(3)
Hospitals, medical care	65	(2)
Shipping, maritime services	51	(2)
Aluminum smelting	46	(2)
Auto repair	46	(2)
Railroad	43	(1)
Lumber manufacturing	42	(1)
Agricultural production crops	33	(1)
Trucking	31	(1)
Fabrication, metal manufacture	27	(1)
Military, national security	27	(1)
Printing, publishing	24	(1)
Federal government	24	(1)
Firefighting station	23	(1)
Hydraulics plant	22	(1)
Logging camp	21	(1)
Colleges and universities	20	(1)
Total	1,796	(64)

Discussion

We have provided an overview of patients seen during a ten-year period at an academically affiliated occupational and environmental medicine clinic. The workplace diversity of clinic patients reflects that seen in Washington State and particularly the greater Seattle area, but it also reflects interest in certain conditions by clinic faculty. For example, asbestos-related lung disease has been an area of research activity for several faculty and trainees, and the large number of patients seen with this condition is due in large part to a selective referral of such patients and follow-up of possible case identification from numerous screening programs.

Our own evolving triage criteria, particular research interests, and subsequent referrals all contribute to limiting the generalizability of this experience to the overall pattern of occupational disease in the local area, let alone the state and region. Moreover, even without the biases introduced by our selection criteria and interests, the same forces leading to the underrecognition and underreporting of occupational diseases in general[10-12] are likely to result in our clinic's experience both underrepresenting and skewing the actual distribution of these conditions in the community. The most prevalent conditions we have diagnosed, however, are remarkably similar to those of another academic referral center in a different geographic region.[9]

Despite limitations in our clinical data base, our descriptive data are nonetheless instructive. Referral patterns indicate that the clinic has been able to respond to diverse sectors in the community, particularly physicians, who sought consultation. The initiation of an occupational musculoskeletal clinic is an example of responding to a perceived need in this area, as identified by patient and physician inquiries. In addition to providing direct patient consultations, the clinic staff responds to countless phone inquiries from physicians and others about hazards and medical effects of exposures.

A substantial proportion of our patients were deemed to have a work-related condition. Although the most common diagnosis, asbestosis, reflects work conditions of many years

past, many identified work-related diseases—such as asthma, acute chemical pneumonitis, and lead poisoning—reflect current hazards. These cases nearly always result in our own efforts at initiating prevention, but they also suggest the potential advantages of linking clinic findings with organized feedback response systems, as suggested by Rutstein and colleagues in describing the benefits of defining and reporting occupational sentinel health events.[13]

Our clinical experiences not only reflect our a priori research interests but have also driven numerous investigations. For example, the evaluation of a patient with chronic encephalopathy that appeared to follow an acute pesticide intoxication was the impetus for ongoing research into chronic neurologic sequelae of pesticide exposures.[14,15] The identification of a cluster of carpal tunnel syndrome in seven grocery checkers spurred epidemiologic studies in grocery checkers and other populations.[16] The clinic has indeed served as a laboratory and has been the basis for numerous faculty and trainee scholarly endeavors.

Clinics such as the one described here also need to be put into the broader context of occupational and environmental disease detection and prevention. There have been important advances in the past several decades in our understanding of the causes and mechanisms of occupational disease. Several approaches are needed, however, to reduce further the incidence and severity of these conditions. In addition to a need for broader surveillance, prevention, and control programs, physicians can play a major role in this effort by diagnosing, treating, and initiating appropriate follow-up of conditions in individual patients. Academically based clinics can fulfill multiple purposes by facilitating the identification of local exposure and disease patterns and by serving as a consultative resource to community physicians. Finally, these clinics can play an important additional role in providing a clinical base for training physicians and other health care professionals in this underserved area of medicine.

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Articles

Controlling a Syphilis Epidemic

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In 1986 the rate of infectious syphilis (primary and secondary) in Los Angeles County began to rise from previously stable levels of about 23.5 per 100,000 to peak at 55.6 per 100,000 in 1987. The incidence of congenital syphilis increased from 205 cases in 1987 to 575 cases in 1989. The county's Sexually Transmitted Disease Program instituted a disease-specific plan to address the epidemic. Factors considered in designing the program included the high morbidity and mortality associated with congenital infection, the existence of latent infection, self-limiting symptoms, and the availability of an inexpensive screening test and curative treatment. Policy changes implemented comprised expanded screening, expanded surveillance, increased contact tracing, and the initiation of condom promotion programs. To evaluate the relative effectiveness of Los Angeles County's syphilis control efforts, the epidemic curve for infectious syphilis was compared with trends in other urban areas. Although the rate of infectious syphilis climbed a year earlier in Los Angeles than in other cities, it returned to baseline levels when other cities' rates remained at epidemic levels.

(Cohen DA, Scribner R, Cory D: Controlling a syphilis epidemic. West J Med 1992 Oct; 157:430-432)

In the shadow of the acquired immunodeficiency syndrome epidemic, the rate of primary and secondary syphilis in Los Angeles more than doubled from 23.5 per 100,000 in 1985 to 55.6 per 100,000 in 1987.[1] An intensive program to limit the incidence of syphilis and congenital syphilis was planned and implemented throughout Los Angeles County. The program addressed the following unique characteristics of syphilis: its self-limiting, painless symptoms and latent stages, so that those infected may not know and have little motivation to seek treatment; the accessibility of an inexpensive screening test; the high morbidity and mortality associated with congenital infection; and the availability of inexpensive, curative treatment.

Background

In 1987 there were about 11,000 cases of syphilis reported in Los Angeles County. Nearly 80% of the 7,144 cases of infectious and early latent syphilis were reported from seven health districts centered around South Central Los Angeles.[2] The rates of infectious syphilis were highest among 25- to 29-year-olds (144.1 per 100,000) and among African Americans (300.6 per 100,000) and Hispanics (42.5 per 100,000). Rates among whites and Asians were 10.3 per 100,000 and 3.1 per 100,000, respectively.[1] The rate of congenital syphilis was 137 per 100,000 births, with African Americans having the highest rate (519 per 100,000) followed by Hispanics (74 per 100,000).[3]

Possible Causes of the Syphilis Epidemic

Several factors may have contributed to the increase in the incidence of infectious and congenital syphilis:

- Countywide screening for syphilis decreased; in the 1980s a serologic test for syphilis was eliminated as a routine screening test and was recommended only when patients admitted to high-risk behaviors.
- A $25 sexually transmitted disease (STD) clinic fee was initiated in 1986, and clinic attendance decreased.
- Staffing of field investigators for the follow-up of syphilis cases decreased.
- "Crack" cocaine appeared, and its use was associated with the "sex for drugs" phenomenon.[5]

Interventions to address three of the four hypothesized contributing factors were developed and implemented. The Los Angeles County Board of Supervisors earmarked an additional $2.7 million for syphilis control and suspended the $25 STD clinic fee.

Interventions

Increase Screening Activities

The STD Program recommended that syphilis screening be performed throughout the county for the following people:

- All women of childbearing age, with pregnant women being screened three times—first and third trimesters and at delivery.
- All sexually active teens.
- All persons with two or more sex partners in six months.
- All persons who use illicit drugs such as cocaine, marijuana, or heroin.
- All persons who have had sex with prostitutes.
- All persons with any other STD or who are positive for the human immunodeficiency virus.

In public health clinics, all new family planning patients and those returning for annual checkups were screened for syphilis. To make an early diagnosis and treat infected women who might not enroll for prenatal care or who might have to wait as long as eight weeks for their first prenatal appointment, it was recommended that all who came in for a pregnancy test also be tested for syphilis. This strategy had been effective in adjacent Orange County in preventing congenital syphilis.[6] In several STD clinics syphilis screening was made available to patients who did not want to wait for an appointment. The capability of clinics to perform immediate rapid plasma reagin tests was assessed and improved.

The prevalence of syphilis was also studied among detain-

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ees at Men's Central Jail in Los Angeles. This was done to determine whether routine or selective screening and empiric treatment should be implemented.

Improve Access to Clinic Services

All of the STD clinics with the highest morbidity were provided with additional staff. This was done to increase the number of patients who could be seen in any given clinic session and to keep the clinic open one evening a week.

Increase Field Follow-up and Improve Surveillance

Additional investigative staff were hired. The Centers for Disease Control also designated Los Angeles County as a training center for public health representatives who do partner notification. Educational programs were developed for nursing staff to improve follow-up skills of postpartum women and infected infants discharged before treatment and evaluation. Nurses had an opportunity to review cases in which there had been a substantial delay in field follow-up,

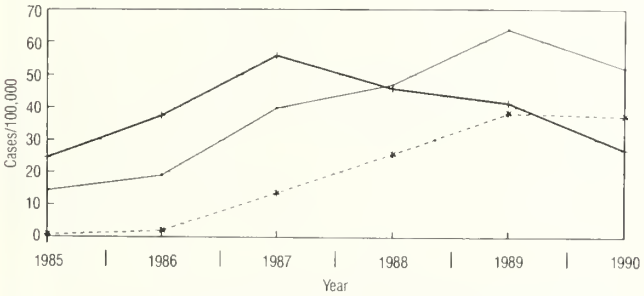

Figure 1.—The graph shows the syphilis rates for Los Angeles County, 1985 to 1990. —•— = early latent, —+— = primary and secondary, - - • - - = congenital (cases/10,000 live births)

resulting in infants with congenital syphilis becoming symptomatic. Through role playing, nurses learned how to handle investigations of possible cases of congenital syphilis in the future. Improved referral and follow-up of infants with congenital syphilis were arranged before hospital discharge, to ensure that the infants would receive a full course of therapy at a local district health center.

Promote Condom Use in Clinics and Increase Health Education Efforts

Before the epidemic, condoms were available in STD clinics but were dispensed at the discretion of an STD clinician. A county policy was developed in which all STD patients were offered ten free condoms at every visit. In addition, the nonlubricated condoms were replaced with condoms lubricated with nonoxynol 9. A health education program in the STD clinic waiting areas encouraged patients to adopt safer sexual practices. Full-time health educators were assigned to five of the clinics with the highest morbidity rates and part-time educators to four other STD clinics. The health educators ensured that the patients would be provided with free condoms, demonstrated how to use a condom, and led discussions about negotiating condom use with sex partners.

Continuing medical education lectures on the epidemiology of syphilis in Los Angeles and on the management of syphilis and congenital syphilis were scheduled at all high-incidence hospitals. Communitywide outreach included lectures at local schools, providing condoms for distribution at local businesses in areas with high morbidity, providing education and condoms to persons enrolled at drug rehabilitation centers, and doing syphilis screening in housing projects and parks in areas with high morbidity.

Methods

To evaluate the effectiveness of the Los Angeles program, secular trends of rates of syphilis in Los Angeles County were examined and compared with rates of infectious syphilis in other urban areas with similar high-risk populations. All comparative data were obtained from the Centers for Disease Control.[7] In addition, several of the interventions were individually evaluated.

Results

Figure 1 shows the rate of cases of infectious, early latent, and congenital syphilis from 1985 through 1990.[2] Initially the rate of infectious syphilis went down while that of early latent syphilis rose. The number of cases of congenital syphilis also rose substantially. In 1990 the rates of both infectious syphilis and early latent syphilis decreased, while that of congenital syphilis remained high.

As shown in Figure 2, in contrast to Washington, DC, New York, and other cities in the United States, the Los Angeles epidemic of infectious syphilis began a year earlier but returned to pre-epidemic levels by 1990. The comparison cities had persistently high rates of syphilis.

Syphilis Screening

Between 1987 and 1989, the number of serologic tests for syphilis performed by the Los Angeles County Public Health Laboratory increased by 45.6%, from 107,458 to 156,505 (R. Barnes, PhD, Director, Public Health Laboratory, oral communication, March 1991). Of the 6,428 women who had pregnancy tests at public health family planning clinics between January and August 1989, 60 had serologic tests reactive for syphilis. Of these, 43 (72%) were diagnosed as new cases of syphilis and, at the time of our review, 33 of the women had been treated for syphilis, potentially preventing

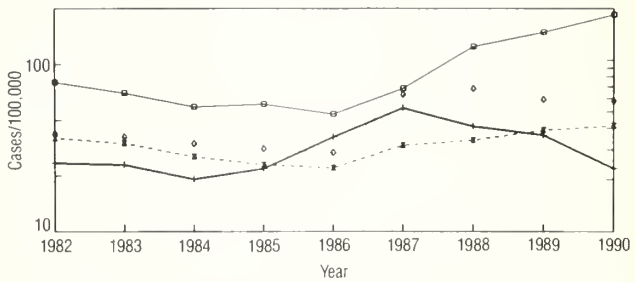

Figure 2.—The graph shows cases of primary and secondary syphilis in selected cities, 1982 to 1990 (from the Centers for Disease Control[7]). —+— = Los Angeles; ◇ = New York City; —o— = Washington, DC; - - ▪ - - = US cities

33 cases of congenital syphilis. A conservative estimate of the rate of syphilis (all stages) among women seeking pregnancy tests at public health family planning clinics is 669 per 100,000 (43 per 6,428).

The screening project at Men's Central Jail documented a 2% rate of untreated syphilis among the 6,217 men tested and booked between 6 PM and 6 AM during the weeks of March and April 1989. The rate of infectious syphilis (primary and secondary) among African Americans was 984 per 100,000 and among Hispanics, 418 per 100,000.[8]

Clinical Services

An intensive evaluation of clinical services was undertaken and audits were done of the following procedures:

syphilis screening guidelines, routine questioning of pregnant women about enrollment in prenatal care, routine questioning of STD patients if they had pregnant partners, availability of immediate syphilis testing, offering ten free condoms to all patients, simplified registration procedures with waiting time reduced to a maximum of an hour, priority given to patients referred as contacts of syphilis patients, elimination of informally established clinician:patient ratios, educational efforts in waiting areas, and evening clinic hours. Clinics were audited four times over the year to see what percentage of the items were implemented by six clinics with high morbidity rates. Each of the clinics improved its compliance with the recommendations, but none were able to adopt all of the recommendations. Decreasing waiting time was the item most frequently failed.

Health educators in each of five districts reached more than 20,000 patients with sexually transmitted diseases. Three methods to promote condom use were compared. One method taught basic condom skills. A second method concentrated on how to convince sex partners to use a condom and eroticized condom use. The third method provided free condoms that were made available to patients at local businesses. Only the first two methods appeared effective with male patients in reducing the rates of STD reinfections, with decreases of as much as 50% compared with controls. None of the interventions were effective with female patients.[9]

Several articles about the syphilis epidemic were published in the local medical society journal.[10-12] There was some short-lived publicity in local newspapers. Also, grand rounds sessions on the epidemic and the management, treatment, and prevention of syphilis and congenital syphilis for physicians were offered at all hospitals, particularly those that had a high incidence of congenital syphilis. About 25 sessions were conducted and were well received.

Discussion

Although the epidemic curve of the syphilis incidence in Los Angeles County is consistent with the establishment of an effective control program, it is impossible to know whether the incidence of infectious syphilis (primary and secondary) decreased as a result of the interventions or if the decrease represented the natural course of the epidemic.[13] During an epidemic, it is impossible to know whether rates will continue to climb, and so action must be taken.

Infectious syphilis rates have risen in many US urban areas through 1990 (see Figure 2). Although they began to decline in 1991,[14] the persistence of high rates in cities like Washington, DC, and New York lends support to the relative effectiveness of the control program in Los Angeles. In contrast to the Los Angeles County Department of Health Services, few other local health departments have been able to provide services for STD treatment gratis or to mount substantial prevention and control measures. Other unique local factors in Los Angeles, such as lower population density, the lack of good public transport, lower rates of HIV infection, and different patterns of illicit drug use, may have offered additional protection against continued syphilis transmission.

Further evaluation of the effectiveness of syphilis control efforts is warranted. Partner notification activities (contact tracing) were the most difficult to assess because they are not uniformly reported by all staff members. Because no summary is kept of the diagnoses of patients visiting STD clinics, it was also not possible to assess to what extent improved access to clinical services contributed to controlling infectious syphilis.

The increased countywide screening efforts likely played an important role in the dramatic increase in the rates of early latent syphilis and congenital syphilis. Several promising screening recommendations targeting high-risk populations, however, were not put into effect. For example, no resources were allocated to continue a screening and treatment program in custody facilities. In 1989 it was calculated that on a daily basis at least eight inmates infected with syphilis at the time of incarceration were released into the community untreated. Since then, it is likely that several thousand men and women have missed the opportunity for diagnosis and treatment. Another study of the incidence of syphilis among this population is crucial to determine whether clinic- and community-based efforts were able to reach this population.

Despite the continued high rates of congenital syphilis, no efforts were made to impose mandatory screening at birth by modifying state law. Specimens of cord bloods should be screened at the time of delivery so that patients with asymptomatic congenital syphilis can be treated and the true epidemic of congenital syphilis can be monitored. Without early treatment, a variety of symptoms, from "snuffles" (bloody nasal discharge) to neurosyphilis, may develop in infants with congenital syphilis and result in mental deficiencies.[15]

In summary, a contemporary syphilis control program should be disease-specific and target high-risk populations. The most intensive screening with rapid treatment of cases should be done among pregnant women, newborns, and women of childbearing age, for whom the consequences of disease are most severe. Other high-risk groups should be targeted: those with few resources and diminished access to health care[16] and those charged with criminal offenses. Screening must be consistent and continue for a period of time beyond the point when the epidemic is contained and rates revert to baseline levels. If screening efforts are reduced too quickly, it is impossible to know whether the subsequent rates of early syphilis are artifactual or reflect an actual decreased incidence of disease.

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Articles

Predicting Risk for Medical Malpractice Claims Using Quality-of-Care Characteristics

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The current fault-based tort system assumes that claims made against physicians are inversely related to the quality of care they provide. In this study we identified physician characteristics associated with elements of medical care that make physicians vulnerable to malpractice claims. A sample of physicians (n=248) thought to be at high or low risk for claims was surveyed on various personal and professional characteristics. Statistical analysis showed that 9 characteristics predicted risk group. High risk was associated with increased age, surgical specialty, emergency department coverage, increased days away from practice, and the feeling that the litigation climate was "unfair." Low risk was associated with scheduling enough time to talk with patients, answering patients' telephone calls directly, feeling "satisfied" with practice arrangements, and acknowledging greater emotional distress. Prediction was more accurate for physicians in practice 15 years or less. We conclude that a relationship exists between a history of malpractice claims and selected physician characteristics.

(Charles SC, Gibbons RD, Frisch PR, Pyskoty CE, Hedeker D, Singha NK: Predicting risk for medical malpractice claims using quality-of-care characteristics. West J Med 1992 Oct; 157:433-439)

Medical malpractice litigation is complex, and other factors besides negligence contribute to the initiation of malpractice claims against physicians. These include characteristics of the physician and the patient, health care systems, and the medical industrial system in which drugs, technology, and equipment are developed and distributed.[1]

It is suggested that a large number of malpractice claims are generated by a few negligent physicians. If this were so, such physicians could be identified and rehabilitated or eliminated from medical practice.[2] Negligence charges, however, are waged against a wide range of physicians, and those in certain specialties are at higher risk for malpractice claims than others.[3,4] In most claims, negligence is not found.[4-6] Nonetheless, certain physicians may possess specific characteristics that render them more "suit prone" than others.[7]

The "fault-based" tort system assumes the history of claims made against physicians is inversely related to the quality of care provided.[8] Actual medical negligence is not easily assessed,[8,9] and evaluating physician-patient interaction is difficult. Characteristics associated with quality health care delivery have been identified, however.[10]

Attributes of Quality Health Care

Donabedian's classic work, which indirectly assesses quality of care in terms of structure, process, and outcome, is the theoretic framework for this study.[10] We structured a spectrum of physician characteristics, distinguishing stable characteristics, such as age and specialty, from modifiable characteristics, such as risk-management behaviors.

Structure

Health care structure consists of relatively stable characteristics of professionals, tools, and resources and the physical and organizational settings in which they work.[10] Attributes affecting a physician's contribution to quality of care are training, experience, specialization,[11] length and appropriateness of training,[12,13] international medical school graduation,[14] volume of similar cases treated,[11] board certification,[13] and organization of the hospital or clinic.[14] Some studies that equated chronologic age with increased experience showed an inverse relationship between increased age and a higher quality of care.[15-17] Rhee noted a curvilinear relationship between years in practice and quality of care, with peak performance occurring from 11 to 15 years in practice.[12]

Structural characteristics linked to a physician's increased claims history include specialty[18] and board certification[18,19] but not international medical graduation.[5,18,19] Physicians in the 45- to 54-year age group, presumably in practice about 15 years, were found to be those most likely to lose their malpractice insurance because of their claims history.[20] In a Florida study, claims experience was not observed to be a valid indicator of physician quality as measured by credentials, disciplinary history, specialty change, or retirement.[18]

Process

The process of care includes interrelated and overlapping activities within and between practitioners and patients.[10] It encompasses the degree of physician competence that patients tend to expect[21,22] and characteristics of the physician-patient interaction.[23]

It might be assumed that technical competence is lacking for claims to occur, but competence is not easily measured objectively,[24] and an award payment to a plaintiff is not a direct indicator that medical malpractice has occurred.[25(p42724)]

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TABLE 1.—*Physician Demographics by Individual Risk Group**

Demographic	Control Group—Low Risk		Sample Group—High Risk			Total
	Group 0 (n=71)	Group 1 (n=49)	Group 2 (n=30)	Group 3 (n=82)	Group 4 (n=16)	(n=248)
Age (mean), yr	46.11	48.35	49.63	52.66	53.56	49.64
Sex, % male	91.3	87.8	96.6	97.6	100.0	93.9
Specialty, %						
Family practice	8.6	20.4	24.1	6.4	7.7	12.1
Internal medicine	27.1	24.5	31.0	11.5	15.4	21.8
Obstetrics-gynecology	2.9	10.2	10.3	19.2	30.8	12.1
Psychiatry	5.7	4.1	--	--	--	2.5
Surgery	27.1	22.4	24.1	55.1	46.2	36.0
Pediatrics	11.4	2.0	3.4	--	--	4.2
Radiology	5.7	6.1	6.9	1.3	--	4.2
Ophthalmology	1.4	6.1	--	1.3	--	2.1
Anesthesiology	5.7	4.1	--	5.1	--	4.2
Additional postresidency training, %	39.4	30.6	40.0	22.0	--	29.4
Board certification, %	85.9	81.6	83.3	87.8	100.0	86.3
International medical graduation	--	2.0	3.3	7.3	6.3	6.5
Current licensure restriction, %	2.8	4.1	--	1.3	6.3	2.4
Emergency department coverage, %	62.3	63.0	69.0	79.0	75.0	69.7
Geographic location, %						
Urban	48.5	41.3	35.7	46.2	68.8	46.2
Rural	25.0	23.9	46.4	26.9	31.3	28.4
Suburban	26.5	34.8	17.9	26.9	--	25.4
Practice type, %						
Single-specialty group	49.3	43.5	48.3	50.0	50.0	48.3
Multispecialty group	8.8	28.3	13.8	18.5	--	15.8
Solo	30.9	28.3	37.9	28.4	43.8	31.3
Health maintenance organizations	1.5	4.3	--	1.2	--	1.7
Hospital-based	13.0	8.7	--	2.5	--	6.2
University	4.3	--	--	--	--	1.2

*Group 0 = no claims; group 1 = ≤3 claims, no payments; group 2 = a single loss of ≥$100,000; group 3 = ≥3 claims, with possible payouts of <$100,000, and group 4 = ≥3 claims, with at least 1 payout of ≥$100,000.

Although a good physician-patient relationship has been suggested as the most effective method of preventing malpractice claims,[26,27] empiric studies have not effectively demonstrated this.[28] In a study that failed to account for the final disposition of claims, sued physicians and suing patients differed significantly in their perceptions of the relationship quality before the filing of a claim.[29]

Outcome

The outcome of care as a measure of quality involves not only the success of treatment or improved health status judged by patient and physician, but also the level of satisfaction perceived by both.[10]

A patient's perception that medical injury has occurred probably plays a major role in whether or not a claim is brought. Physicians' personalities, behavior patterns, general health, and professional satisfaction influence quality of care[10] and may contribute to claims history. For example, a group of Oregon physicians disciplined for inappropriate prescribing were found to have significantly more malpractice claims than a control group.[30] There are no studies linking physician impairment to claims history.[2]

Study Rationale

Surgical specialty,[18,31] board certification,[18,19] and emergency department coverage,[1] all structural attributes of care, bear strong relationships to claims history. A recent study that attempted to identify physicians with distinct error profiles found only specialty consistently associated with error type.[31] Our study was designed to assess further the relationship between the physicians' claims history, whether or not legal settlement was reached or negligence was assessed, and the selected physician characteristics associated with quality care. We identified the characteristics associated with increased or decreased risk for claim and the possibility of modification or change in the identified characteristic.

Method

The sample consisted of physicians identified as "high risk" from a list generated by mandated reports of medical malpractice claims (from 1972 to 1988) to the Oregon Department of Insurance and Finance. A claim was defined as a written demand for compensation or services, irrespective of associated litigation. Physicians were defined as high risk who had a single loss of $100,000 or more (group 2), three or more claims that, in some cases, resulted in payouts of as much as $100,000 (group 3), or three or more claims with payouts of more than $100,000 (group 4). We randomly selected 236 of the 315 physicians identified. A control group of 219 physicians was randomly selected (every 14th name) from the balance (3,075) of the Oregon Medical Association membership list.

Using basic survey methods,[32] a refinement of an instrument employed in previous studies[33,34] was mailed to both groups; confidentiality was assured, and responses were coded. Because some physicians in the control group acknowledged previous claims, the control group was further divided into two groups: group 0, those who had never had a

claim, and group 1, those who had a claim but did not meet high-risk criteria (Table 1).

Instrument

An 11-page self-report questionnaire examining areas of physicians' personal and professional characteristics was used. Questions were grouped according to Donabedian's framework for assessing quality of care.[10] Some of these characteristics encompassed two categories, that is, process and outcome,[10] but for the purposes of analysis, we assigned an item to only one category. We classified survey items as follows: structure of care: demographic data, credentials, practice characteristics including patient contact hours (patient volume), and hours of professionally related non-patient activities; process of care: practice-related behaviors and procedures, often defined under the rubric of risk management, including aspects of the physician-patient interaction; and outcome of care: measures of physician satisfaction, attitudes toward practice and profession, and a list of physical and emotional symptoms, including a standardized assessment of alcohol history,[35] reflecting the health status of the physician. Sections were included on the claims history and an inventory of coping strategies that physicians used during litigation.

Statistical Methods

In a preliminary data analysis, responses of five groups of physicians were compared using χ^2 statistics for categoric variables and one-way analysis of variance for continuous variables, and individual pairwise group differences were computed using Duncan's multiple range test.

Variables used in the second stage of analysis were empirically derived based on a statistical consideration of the exploratory analysis that is theoretically consistent with Donabedian's framework (Table 2). The sample was analyzed to test the prediction of low risk (groups 0 and 1) and high risk (groups 2, 3, and 4). Owing to the composition of this study population, variables such as sex (n = 15 women), international medical school graduation (n = 16), and license restrictions (n = 6) were excluded because of low numbers. Age and specialty defined as medical (family practice, internal medicine, pediatrics, and psychiatry) and surgical (obstetrics and gynecology, surgery, ophthalmology, radiology, and anesthesiology) were included in each analysis.

Each of the remaining 34 variables relating to a component of Donabedian's framework was tested in a series of five logistic regression equations (one for each of the five listed in Table 2). For the physician attitude and emotion subarea (see Table 2), the five attitudinal measures were derived from a factor analysis of 24 attitudes toward practice (Table 3).[36]

Variables found significant in individual logistic regressions within each Donabedian component area were combined into a single logistic regression analysis. (For individual paired between-group comparisons, only variables for which significant overall group main effects were found were further analyzed [see Table 5].) After the parameter estimation phase, physicians were classified as low or high risk based on the estimated logistic regression model, testing accuracy in the classification of the logistic regression model. To determine generalizability of the estimated model, a random sample of two thirds of the physicians was used in the estimation phase; the remaining third was used during the classification phase only. Thus, the estimated model was not influenced by the data of the smaller subsample. Classification of this subsample provided an index of how well the estimated model predicted risk in an independent sample of physicians.

Results

There were 248 completed surveys (54.1% response rate). Response rates above 50% were considered acceptable given the nature of the survey population and the content and length of the questionnaire.[4,32] Demographics and practice characteristics of the study group are shown in Table 1. Comparison with nonrespondents, physician population in the same state, and physician population in the nation is shown in Table 4. Although nonrespondents' board-certification data were not available, they are similar to study group members on other demographic characteristics. The study group appears to have fewer women but a higher proportion of board-

TABLE 2.—*Physician Characteristics Using Donabedian's Framework**

Structure		Process		Outcome
Demographics	*Practice Characteristic*	*Practice Related Behaviors*	*Practice Procedures*	*Physician Attitude and Emotions*
Age	Location	Risk management education	Allows patient input	Conflicted attitude
Specialty	Practice-type	Risk management behaviors	Schedules enough time	Satisfied attitude
Sex	Emergency department coverage	Days ill	Follow-up procedures	Naive attitude
Postresidency training	Patient-care hours	Days out	Calls served by clerk	Unfair attitude
Board certified	Nonpatient hours		Calls served by nurse	Needy attitude
International medical graduate	No. of times changed location		Calls served by MD	Emotional symptoms
License restriction			Office record documentation	
Marital status			Informed consent: charted	
			Informed consent: signed by patient	
			Informed consent: verbal	
			Sign out to same specialty	
			Sign out to other specialty	
			Sign out to nurse	
			Sign out, beeper or telephone	
			Accepts any patient	
			Screens patients	

*From Donabedian.[11]

TABLE 3.—*Factor Analyticolly Derived Scales Reflecting Attitudes Toword Practice*

	Conflicted	*Sotisfied*	*Unfoir*	*Noive*	*Needy*
	Medicine is different from 5 years ago	With referral options	Most claims are unjustified	Less experienced get sued	Important to be liked
	Patients expect too much	With coverage arrangements	Claims do not represent malpractice	Less knowledgeable get sued	Claims are part of job
	I practice defensively	With backup from staff	Physicians not guilty still get sued		Want my patients to like me
	Difficult to uphold ideals	With backup from peers			
Eigen value*	3.766	2.348	2.094	1.566	1.342
Variance, %	15.7	9.8	8.7	6.5	5.1

*From Harman.[36]

certified physicians than expected compared with state and national data. International medical graduate representation in the study sample is comparable to the same state sample but is lower than the US physician population in general. In all four populations, internists and family practitioners constitute approximately a third of the physician population. The study group is comparable to state and national physician populations and does not contraindicate generalizability of the results.

Preliminary and Intermediate Analyses

Individual risk groups differed from one another on a list of characteristics and attitudes for which an overall significant main effect of a group was found at the 5% level (Table 5). The table construction indicates a direction so that the horizontal group designation represents a significantly "more likely" or "greater" function than the vertical group designation. For example, physicians in group 3 were significantly more likely than groups 0, 1, and 2 to be in a surgical specialty.

TABLE 4.—*Comporison of Sample, Nonrespondents, Stote, and United States Physicions*

Independent Voriobles	*Respondents (n=248)*	*Nonrespondents (n=207)*	*Oregon Stote Medicol Society*	*US Stotistics*
Age (mean), yr	49.64	50.42	45.9	44.0
Sex, %				
Male	93.9	91.3	86.8	85.4
Female	6.1	8.7	13.2	14.6
Specialty, %				
Family practice	12.1	20.3	18.5	12.1
Internal medicine	21.8	13.0	14.5	16.4
Obstetrics-gynecology	12.1	8.7	5.6	5.6
Psychiatry	2.5	1.9	6.2	6.2
Surgery	36.0	30.9	20.5	23.2
Pediatrics	4.2	3.9	5.1	6.4
Radiology	4.2	4.8	4.3	1.8
Ophthalmology	2.1	1.4	3.4	2.7
Anesthesiology	4.2	8.2	5.5	4.0
Board certification, %	86.3	--	--	53.4
International medical graduation, %	6.5	7.8	7.4	21.5

Separate logistic regression analyses were done for measures in each Donabedian component with risk group (low or high) as the dependent variable. Age and specialty were included in each analysis and were statistically significant, with increased age and surgical specialty predictive of high risk. Additional significant results served as the basis for the final analysis.

Final Analysis

A logistic regression equation was developed based on the 11 variables that most accurately (73.9%) classified subjects into risk group (Table 6). Significant predictors of the high-risk group include increasing age, surgical specialty, emergency department coverage, increased number of days away from practice for vacation or out-of-town meetings, or both, and feeling that the current climate of litigation is "unfair." Low-risk group membership is predicted by a greater degree of current emotional symptoms, routinely scheduling time for patients to talk about their concerns and taking patients' calls directly, and feeling satisfied with practice arrangements.

To test the generalizability of our model, parameters were estimated on a two-thirds random subsample (n = 128) and applied to the remaining third (n = 71), resulting in a correct classification of 77.5% of the remaining third sample, with a false-positive rate of 21.4% and a false-negative rate of 24.1%. Sensitivity of the measure was 82.5% and specificity was 71%.

Prediction of Risk Group: Years in Practice

Increasing age emerged as the strongest predictor of being in the high-risk group. Because previous research on quality of care suggested that peak physician performance occurred at about 15 years in practice, predictive accuracies were calculated for physicians who had been in practice 15 years or less and those who had been in practice more than 15 years, based on the previously estimated function for the two-thirds sample and applied to the third that was not used in estimating the weights.

Predictive accuracy for those in practice 15 years or less was 90.9% (false-positive rate of 6.7% and false-negative rate of 11.1%). We were able to predict accurately the risk group of 66.7% of the physicians in practice more than 15 years (false-positive rate 29.6%, false-negative rate 41.7%).

To explain the greater predictive accuracy of the 15 years or less group, the relationship between years in practice and each of our predictor variables was examined. As expected, those physicians who had been in practice a shorter time were significantly younger than those in practice more than 15 years ($t = 16.9$, $df = 238$, $P < .001$). They also spent more time in direct patient care ($t = 2.5$, $df = 239$, $P < .01$) and in non-patient-related professional activities ($t = 1.82$, $df = 237$, $P < .10$) and reported more satisfaction with their practice arrangements than their older colleagues ($t = 2.9$, $df = 229$, $P < .01$). The over-15 years group was more likely

to have taken a risk-management course ($\chi^2 = 2.75$, $df = 1$, $P < .10$) and to take patients' calls directly rather than have them served by office personnel ($\chi^2 = 7.00$, $df = 1$, $P < .01$). The groups did not differ significantly on the remaining predictor variables.

The relationship between years in practice and ability to classify physicians correctly into high- and low-risk groups was contrasted on predictor variables for those in practice 15 years or less and more than 15 years. As noted, predictive characteristics for low- and high-risk grouping for those in practice less than 15 years resemble those for the full sample but differ from those in practice more than 15 years (Table 7).

Discussion

Nine characteristics, representative of three components of Donabedian's framework to assess quality of care, were associated with a physician being at low or high risk for malpractice claims. Cross validation in an independent sample of physicians (one-third random sample) revealed these findings were not due to chance association produced by looking at a larger number of variables.

Of the nine characteristics, surgical specialty is the strongest predictor for being at high risk for claims. This finding coincides with insurers' underwriting experience and with recent literature about malpractice litigation,[18,31] including the fact that surgeons engaged in high-risk or invasive work, or both, have been found to have higher rates of claims but not necessarily higher rates of negligence.[8] Why might this be so? The work itself may explain surgeons' claim vulnerability. Patients' expectations may differ for surgical, in contrast to medical, interventions. The amount of risk increases in complicated, often traumatic surgical situations in which unexpected adverse events are capable of producing serious injury or death. The fact that in our study surgeons in practice more than 15 years who also had desirable practice behaviors, especially those associated with good risk management, are at greatest risk suggests that surgical work stands alone as a significant risk factor. A claim in many of these instances may represent an unusual occurrence, an untoward outcome, or a single deviation from a physician's usual practice of otherwise high-quality care. Our study confirms Brennan and co-workers' assessment that efforts to identify "bad physicians" by a review of malpractice claims appears to be unproductive.[8]

Brennan and associates found in their review of paid claims that, aside from specialty, no other physician characteristics were associated with particular error profiles.[8] Our study, using both paid and unpaid claims, although confirming strength of specialty as a predictor, also found another structural characteristic, that of increasing age, as important to the risk stratification process.

We found that risk-for-claims differences are a function

TABLE 5.—*Comparative Profile of Individual Risk Groups**†

Independent Variables	*Group 0*	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*Overall, P*
Age	3,‡4‡	3‡	--	--	--	<.001
Specialty (surgical vs medical)	3§	3§	3§	--	--	<.001
Location	--	--	--	--	--	<.05
Emergency department coverage	3‡	3‡	--	--	--	--
No. of times changed practice	1‡	--	--	1‡	--	--
Schedules enough time	--	2,‡3‡	--	--	--	--
Informed consent charted	2‖	2‡	--	2‡	2‡	<.05
Informed consent signed by patient	--	--	0‡	--	0¶	--
Informed consent verbal	--	--	0‖	0‡	0‡	<.01
Sign out to nurse	--	--	0,‡3‡	1‡	--	--
Conflicted attitude	--	3,‡0‡	--	--	--	<.05
Unfair attitude	3‡	--	--	--	--	--
Needy attitude	3,‡1‡	--	--	--	--	<.01
Risk-management education	3§	3‖	--	--	--	<.05
Days ill	2‡	2‡	--	2‡	--	--
Days out	4‡	4‡	--	4‡	--	<.05
Emotional symptoms	--	--	0,‡1‡	--	0,†1†	<.01
Being sued is an occupational hazard	--	0§	0‖	--	0†	<.01
Satisfied with career in medicine	--	--	--	1†	0,‖1,‖2,‡3‡	<.01
Difficult to uphold ideals	--	--	--	1‡	--	
Patients' expectations are too high	1‡	--	1‖	1‖	1‖	<.05
Patients get higher quality of care than 5 years ago	--	3§	0,‡3§	--	3‡	<.001
Plans to retire early	3§	--	--	--	--	<.01
Risk management helps prevent losses	--	--	3‡	--	--	--
Experienced death of a parent	3§	3‡	--	--	3¶	<.001
Experienced death of own child	3‖	3¶	--	--	--	<.05
Marital status						
Married	3‖	3,‖2‡	--	--	--	<.01
Divorced	--	--	--	4¶	--	<.01
Sex, male	--	3,‡4¶	--	--	--	--

*The numbers in the horizontal categories represent the group(s) in which the variables were more likely to be true compared with the groups in the vertical categories. Group 0 = no claims; group 1 = ≤3 claims, no payments; group 2 = a single loss of ≥$100,000; group 3 = ≥3 claims, with possible payouts of <$100,000; and group 4 = ≥3 claims, with at least 1 payout of ≥$100,000.

†The complete list of variables examined is presented in Table 2. Only variables for which significant between-group differences were found are presented here.

‡$P<.05$. §$P<.001$. ‖$P<.01$. ¶$P<.10$.

TABLE 6.—*Predicting High Risk: Results of Logistic Regressions in Complete and Two-thirds Sample*

Independent Variables	*Final Equation (Full Sample)*	*Final Equation (⅔ Sample)*
Structure attributes		
Age	0.0743*	0.0902*
Specialty	1.1361†	1.1082‡
Emergency department coverage	0.9049‡	0.7292
Nonpatient-care hours	−0.0298	−0.0346
Process attributes		
Days out	0.0283‡	0.0352‡
Schedules enough time	−0.5516†	−0.4123
Calls served by physician	−0.8748‡	0.9163§
Informed consent signed by patient	−0.6036†	−0.5566
Outcome attributes		
Satisfied attitude	−0.1382§	−0.1364
Unfair attitude	0.1761‡	0.1053
Emotional symptoms	−0.1652‡	−0.1754‡
Classification accuracy, %	73.9	72.7

*$P<.001$ †$P<.01$. ‡$P<.05$. §$P<.10$.

comes" not yet named in a claim but fearful such an event could occur.

Our study results raise two other questions: do "good" risk-management efforts by high-risk physicians in practice more than 15 years bear any relationship to the "location" of claim-producing incidents, and, if so, what educational interventions could be undertaken to counteract these risks? For example, although emergency department coverage was a structural characteristic associated with a high risk for claims among those in practice less than 15 years, it was not for those in practice more than 15 years. Perhaps the latter group eliminates emergency department coverage around that time, or perhaps increased years of experience in this setting partially immunize them from exposure to claims. Whatever the cause, focused risk-management efforts with physicians in practice less than 15 years might be beneficial, especially in emergency departments.

We conclude that selected structural, more stable, physician characteristics are particularly significant predictors of claim vulnerability. Brook and associates' conclusion that structural characteristics are not good predictors of quality[37,38] highlights our results and leads to the suggestion that the relationship between medical malpractice claims and quality care may be of a different order than originally thought. The hypothesis that a relationship is observable between claims history and selected physician characteristics associated with quality of care is supported by this study. The fact that older physicians generally practice "good" risk-management behaviors and remain vulnerable to claims impels us to identify further those practice characteristics subject to modification that can be implemented in practice. If the practices of the general population of physicians can also reflect good risk-management behaviors, the relationship between claims vulnerability and quality of care can be better assessed.

TABLE 7.—*Significant Predictors for Low and High Risk for Claims*

*Full Sample**	*Physicians in Practice,† χ^2* ≤ *15 Years*	*Physicians in Practice,† χ^2* > *15 Years*
High risk	High risk	High risk
Increased age	Increased age‡	Surgical specialty‡
Surgical specialty	Surgical specialty§	Risk-management education‖
Emergency department coverage	Emergency department coverage	Schedules time to talk to patients
More days away from practice	More days away from practice¶	More risk-management prescribed behaviors§
"Unfair" attitude	Risk-management education¶	
Low risk	Low risk	Low risk
More emotional symptoms	More emotional symptoms‖	Verbal consent§
Schedules time to talk	Signed§ or verbal consent¶	
Answers patients' calls directly	"Unfair" attitude§	
"Satisfied" attitude		

*Described in Table 6 and based on logistic regression. †χ^2 analysis and analysis of variance were used. ‡$P<.001$ §$P<.05$. ‖$P<.01$. ¶$P<.10$.

of increasing age until physicians have been in practice about 15 years. After that, age ceases to be a significant predictor of risk. This plateau effect has important implications. Until now, it was thought that risk increased directly with years in practice because of increased exposure to possible adverse consequences. Our data suggest that the effect of increasing age is limited. It peaks not at the end of a physician's career but at about 15 years, a period, it has been suggested, when the highest quality of care is provided.[12] It is not surprising that this is also the time when physicians are most likely to lose their malpractice insurance because of adverse claims.[20]

Practice characteristics associated with the low-risk group also fit the pattern of common suppositions about malpractice claims; when physicians engage in behaviors to increase communication and patient comfort, risk for claim is diminished. These behaviors tended to be associated with the process and outcome of care, such as scheduling more time to talk with patients, answering patients' calls directly, and satisfaction with practice arrangements. Why physicians in the low-risk group who implement these behaviors also suffer significantly more emotional symptoms than their high-risk counterparts is unclear. They, for example, may represent "worried well" physicians involved in occasional "bad out-

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* * *

VISITING HOURS

She is shrinking, telescoped into her body.
Her face writes its own history.
She is spoon-fed, diapered, turned
this way and that—the shell preserved.
Her husband remembers her as silk damask.
Her children wait for an avalanche of recognition.

She has emptied the pockets of memory.
Show her old photographs.
Say that her grandson has her eyes,
that he has graduated cum laude,
that she will come home again.
Reach her with the divining rod of love.

She smiles fleetingly.
Words drop like apples from a tree.
Spidery fingers clutch the doll in her lap.
The woman she has left behind is a stranger.
She is an empty room,
the door shut against intruders.

MARY ENGEL©
North Bergen, New Jersey

Conferences and Reviews

Overwhelming Postsplenectomy Infection
Still a Problem

MALCOLM L. BRIGDEN, MD, FRCPC, *Victoria, British Columbia*

Despite an extensive medical literature over the past ten years, patients continue to die needlessly of overwhelming postsplenectomy infection. Although physicians have become increasingly cognizant of this syndrome in children, many remain unaware of the risk to asplenic or hyposplenic adults with no underlying medical problems. In addition, many older asplenic or functionally hyposplenic persons are unaware that they are at risk for this syndrome. The identification of Howell-Jolly bodies on a peripheral blood smear should alert physicians to the need for further follow-up to establish hyposplenism and to consider possible antipneumococcal vaccination.

(Brigden ML: Overwhelming postsplenectomy infection—Still a problem. West J Med 1992 Oct; 157:440-443)

A 36-year-old man presented to an emergency department at 6:30 PM with a half-day history of flulike symptoms. There was a history of splenectomy at age 5½ because of hereditary spherocytosis. The patient had not received the pneumococcal vaccine. He appeared fine on leaving for work at 6 AM, but came home at 1:30 PM complaining of feeling poorly with malaise and myalgias. By 3:30 PM the patient was febrile (39.5°C) with vomiting, diarrhea, and lower back pains.

In the emergency department, the patient was hypotensive and oliguric with a blood pressure of 80/40 mm of mercury and a temperature of 40°C. On examination he was mentally confused and appeared "shocky" and cyanotic with several large purpura on the trunk and petechiae on both lower extremities. A blood gas determination documented metabolic acidosis, and hematologic investigations suggested the presence of disseminated intravascular coagulation. A tentative diagnosis of septic shock due to postsplenectomy infection was made. Vigorous treatment with hydration, large doses of penicillin, steroids, a dopamine infusion, and blood component therapy was promptly instituted. Despite these therapeutic measures, the patient died three hours after hospital admission. Autopsy findings were compatible with the Waterhouse-Friderichsen syndrome, and all antemortem blood cultures subsequently showed *Streptococcus pneumoniae*.

Clinical Features and Incidence

The common clinical features of overwhelming postsplenectomy infection (OPSI) are outlined in Table 1.[1-4] As the case history illustrates, few infectious states can proceed as rapidly in apparently healthy persons. Although meningitis or pneumonia may accompany OPSI, in many patients there is no obvious site of bacterial colonization, and a cryptic source in the nasopharynx is frequently postulated. The initial prodrome is typically mild and nonspecific with flulike symptoms. These may include fever, malaise, myalgias, headache, and vomiting. This initial prodrome is usually followed by a rapid evolution to full-blown bacteremic septic shock accompanied by hypotension, anuria, and clinical evidence of disseminated intravascular coagulation. Severe hypoglycemia may be present. The subsequent clinical course frequently mirrors that of the Waterhouse-Friderichsen syndrome, and bilateral adrenal hemorrhages may be found at autopsy. Despite intensive therapeutic intervention, the overall mortality as published in older studies for establishing cases varied from 50% to 70%.[1] More recent information suggests that if informed patients seek medical attention promptly, mortality may be reduced to the 10% range.[5] Of those patients who die, more than 50% do so within 48 hours of admission to hospital.[1]

The infecting organisms characteristically are encapsulated.[1-3] The organism most frequently implicated has been the pneumococcus (*S pneumoniae*). This organism has been implicated in roughly half of all reported cases. *Haemophilus influenzae*, meningococcus (*Neisseria meningitidis*), and group A streptococci have accounted for an additional 25% of infections. Less frequent pathogens include *Staphylococcus* species, *Pseudomonas* species, or other gram-negative organisms.[3] Recently the fastidious bacterium DF-2 (*Capnocytophaga canimorsus*) has been identified as a pathogen responsible for OPSI following dog bites.[6] Frequently bacterial proliferation in OPSI is so extreme that bacteria may be seen in buffy-coat preparations or remarkably in the polymorphonuclear leukocytes present on smears made from unspun peripheral blood.[7] The precise incidence of OPSI remains controversial because published estimates vary considerably. The most reliable data, reported by Schwartz and co-workers, were derived by applying actuar-

TABLE 1.—*Clinical Features of Overwhelming Postsplenectomy Infection*

Cryptic infection (no obvious focus)
Short, nonspecific prodrome
Massive bacteremia with encapsulated organism
Septic shock with disseminated intravascular coagulation
Marked virulence: 50% to 70% mortality
Death ensues in 24 to 48 hours

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ial methods to a population free of selection bias and with accurate long-term follow-up.[8] This study estimated that the risk of fulminant infection was reasonably low, in the range of 1 case per 500 person-years of observation. The overall cumulative risk of infection requiring admission to hospital, however, was 33% by the end of a ten-year follow-up after splenectomy. Following splenectomy in childhood, the incidence is probably greater, in the range of 1 fatal case of OPSI for 300 to 350 patient-years of follow-up.[1] Because most of the published data antedate the availability of the pneumococcal and *H influenzae* vaccines, the current overall incidence of OPSI is likely to be lower than these published estimates.[2,3]

Factors Predisposing to Overwhelming Infection

The single most important factor in the pathophysiology of OPSI appears to be the vital role of splenic macrophages in dealing with encapsulated organisms.[1,2] It is clear from the medical literature, however, that the predisposition of asplenic and hyposplenic persons to infection varies with the patient population examined and the underlying disease status.[3]

The age at which splenectomy occurs is an important consideration.[1-3] Although adults are not immune from OPSI, children are clearly at greater risk, especially those younger than 2 years. This is probably related to the fact that the coating of bacteria with opsonizing antibodies and the tortuous splenic microcirculation are key factors in the effective phagocytosis of encapsulated organisms. Infants do not acquire specific antibodies against encapsulated organisms until relatively late in the development of the normal range of antibody responses.

The reason for splenectomy also appears to be a key factor.[1,2] Splenectomy performed for a hematologic disorder or lymphoma appears to carry a much higher risk than splenectomy performed as a result of trauma. Although part of this may be related to the immune status of the patient, a major factor is probably the occurrence of splenic implants (splenosis) or accessory spleens in traumatized patients.

The time interval from the date of splenectomy is also important. Several studies have shown that most admissions to hospital for serious infections occur within the first two years.[4] For instance, in young children who have had a splenectomy, 80% of OPSI cases occur within this time frame. It must be emphasized, however, that some degree of risk persists for all of adult life. There are case reports of OPSI occurring as long as 42 years after a splenectomy.[9]

The presence of splenic implants or accessory spleens is also a major risk modifier. Small implants of splenic tissue in the peritoneum are found in about 50% of patients who undergo splenectomy for trauma, an event known as splenosis.[2,3] About 10% of these patients have accessory spleens. There is both experimental and clinical evidence that regenerative splenic tissue can be protective even if the amount of residual tissue is only a small fraction of the normal organ mass.[10] The degree of protection appears to be variable and unpredictable, however. A number of reported cases of OPSI have occurred in the face of remaining splenic tissue or splenic implants.[11]

The overall immune status of a person is also important.[1-3] Conditions that are known to be associated with defects in cellular or humoral immunity such as Hodgkin's disease or hypogammaglobulinemia can have a major effect on a person's ability to mount an effective antibody response to foreign antigens or infection.

Identifying Risk in Patients

Although patients who are known to have had a splenectomy for hematologic disease or trauma may be readily apparent, there exists a population of persons who suffer from functional hyposplenism or may not be aware that their spleens were removed during gastric or hiatal hernia repair.[3] In addition, although rare, the spleen may be congenitally absent, especially in association with certain cardiac malformations.[1]

The wide variety of diseases that have been linked with functional hyposplenism is shown in Table 2.[1-3] Although many of these conditions are rare, certainly the association in some patients with relatively common conditions such as severe liver disease, celiac disease, ulcerative colitis, or systemic lupus erythematosus merits clinical attention. In addition, patients undergoing high-dose steroid therapy or splenic irradiation as part of cancer therapy may have impaired splenic phagocytic activity and face an increased risk for OPSI.[12] Functional hyposplenism has also been reported as a late complication of allogeneic bone marrow transplantation complicated by extensive graft-versus-host disease.[13]

TABLE 2.—*Conditions That May Be Associated With Hyposplenism*

Type	*Disorder*
Gastrointestinal	Celiac sprue
	Dermatitis herpetiformis
	Ulcerative colitis
	Liver disease—portal hypertension
Immunologic	Systemic lupus erythematosus
	Rheumatoid arthritis
	Graves' disease
	Polyarteritis nodosa (splenic infarct)
Infiltrative	Thorium dioxide (Thorotrast) administration
	Amyloidosis
	Sarcoidosis
Miscellaneous	Sickle cell disease
	After bone marrow transplantation
	Cancer therapy
	?High-dose steroid therapy
	?Splenic irradiation

Fortunately, a hematology laboratory can play a major role in identifying patients at risk. A consistent abnormality reflecting hyposplenism or asplenia is the presence of Howell-Jolly bodies.[3] These small, round remnants of the original erythrocyte nucleus are readily apparent on microscopic examination of a peripheral blood smear (Figure 1). Although some of the newer automated hematology analyzers may on occasion flag Howell-Jolly bodies, if any question of asplenia or hyposplenism exists, the clinician should always request a standard blood smear review. The finding of Howell-Jolly bodies in a peripheral blood smear, although not sufficiently sensitive for the detection of minor degrees of hyposplenism, can identify a degree of hyposplenism that presents a risk for OPSI.[14] One reference laboratory processing more than 100,000 peripheral blood smears per year reported an incidence of new patients showing Howell-Jolly bodies of 1 per 200 or 0.5%.[15] Many of these patients and their physicians were unaware of their asplenia or hyposplenism. When Howell-Jolly bodies are noted on a peripheral smear, the laboratory should clip a note to the report

form informing the patient's physician of the possible presence of hyposplenism. Practicing physicians in turn must be alert for the appearance of Howell-Jolly bodies and follow up on any patients in whom this abnormality is reported for asplenia or functional hyposplenism. If any question exists as to the physical presence or functioning of the spleen, a radionuclide spleen-liver scan may be of benefit.

Measures to Prevent Overwhelming Infection

With a growing appreciation of OPSI, splenic surgery has become increasingly conservative.[16] The trend seems to be to avoid splenectomy whenever possible by observing patients with confirmed isolated splenic rupture and using blood transfusions appropriately. In one such protocol, surgery is not done if the hematocrit becomes stable during the first 24 hours and transfusion requirements do not compromise more than a third of the blood volume.[17] New surgical procedures such as splenorrhaphy or partial splenectomy have been developed that will often allow the spleen to be preserved or repaired.[18] Another surgical approach is splenic autotransplantation into the mesentery, but the overall effectiveness of this procedure is still being evaluated.[19]

A major breakthrough in the prophylaxis of patients at high risk for OPSI has been the introduction of an effective

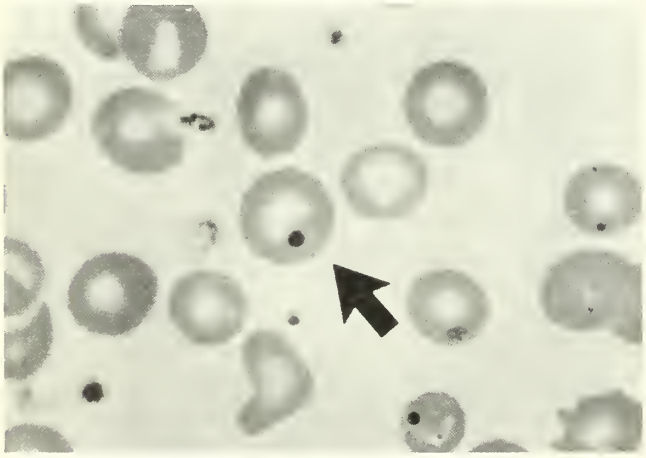

Figure 1.—The presence of Howell-Jolly bodies (arrow) on the peripheral blood smear is suggestive of asplenia or hyposplenism.

polysaccharide vaccine for *S pneumoniae*.[20] This vaccine currently contains purified capsular material from 23 of the most prevalent types of *S pneumoniae*. It has been estimated that these 23 bacterial types are responsible for 90% of the bacteremic pneumococcal disease seen in North America.[21] Because the vaccine comprises 23 independent polysaccharide antigens, about 10% of possible antibody responses to individual antigens unfortunately do not occur. This partially explains the fact that cases of OPSI have occurred in those who have received the vaccine.[22] Young children, persons with neoplastic disease, and those who are immune compromised or receiving immunosuppressive therapy are the least likely to be protected by the vaccine.[23] For instance, new patients with Hodgkin's disease should be vaccinated at least two weeks before therapy to allow for an adequate antibody response. If vaccination is delayed until after treatment has begun, inadequate antibody responses are observed for as long as three years.[24]

The administration of the pneumococcal polysaccharide vaccine appears to carry minimal morbidity.[20] Vaccination should not be done during a febrile illness. In a pregnant woman, vaccination should generally be deferred, and in any patient the possible risks of infection should be weighed against any possible hazards associated with the vaccine. About 30% of patients have minor side effects including erythema, myalgia, or mild induration with localized pain at the injection site; 3% to 7% of patients have mild pyrexia for 24 to 48 hours after vaccination. Severe systemic reactions with photophobia, chills, and high fever occur with only 1 in 1,000 vaccinations and usually resolve spontaneously. The duration of protective antibody levels is at least three to five years in most nonimmunosuppressed persons.[20]

The official recommendation for most patients had been for a single pneumococcal vaccination because of an increased incidence of local reactions initially reported following revaccination. Recent guidelines, however, have suggested that high-risk patients such as those without spleens should now be considered for revaccination after three to six years. This is especially the case if they received the earlier 14-valent vaccine rather than the current 23-valent preparation or there is reason to suspect that their antipneumococcal antibody levels have declined substantially.[25]

Most recently vaccines for *H influenzae* and meningococcus groups A and C have become available. Some authorities have also advocated providing these on a routine basis to all asplenic or functionally hyposplenic younger patients.[26,27] Unfortunately, the protective efficacy of these vaccines has not been as great as that associated with the use of the pneumococcal vaccine, and most trials have been in healthy persons rather than patients undergoing splenectomy.[28]

As noted earlier, sporadic cases of pneumococcal vaccine failure have been reported in appropriately immunized persons. In addition, other bacteria account for at least 50% of OPSI cases. For these reasons, vaccination by itself should not confer a false sense of security. Besides vaccination, patients who have lost their spleens or have functional hyposplenism must be made aware of the possibility of OPSI. The advice given should be simple, clear, and nonalarmist.[29] All such persons should wear a Medic Alert bracelet* detailing their condition.

Patients should be advised that if they become acutely ill, they should report symptoms that might otherwise be dismissed as "the flu" to their physicians.[1,2] In this situation, a possibility is to admit such patients to the hospital immediately and obtain appropriate cultures. While the microbiology status remains uncertain, intravenous antibiotic therapy could be commenced, or as an alternative, the patient may be closely observed.[3] If it is elected to use antibiotics, penicillin is probably the drug of choice for adults, in whom *S pneumoniae* or *N meningitidis* is frequently responsible for infection. Another drug such as ampicillin or a third-generation cephalosporin would be required for children in whom *H influenzae* or gram-negative organisms may be present. If no evidence of progressive infection is noted and microbiologic workup is negative, the patient may be discharged after an observation period of 8 to 12 hours.

Some authors have advocated giving patients their own supply of an antibiotic such as ampicillin, to be taken at the first sign of a respiratory illness, fever, or rigor, especially if there is likely to be any delay in medical evaluation.[30] There is currently no definite proof that such early treatment will

*Medic Alert, 1000 N Palm, Turlock, CA 95380.

lower the incidence of OPSI.[1,2] The literature series with the lowest mortality reported to date emphasized patient education, close follow-up, and prompt medical advice at the earliest sign of even minor infection.[5]

A suggestion has also been made that prophylactic ampicillin therapy be given twice a day for two years or longer to all patients immediately after they have had a splenectomy.[31] Although pediatricians frequently provide antibiotics for asplenic patients younger than 2 years, the value of such an approach in older children and adults has not been adequately evaluated by clinical trial. Compliance is always a major problem with prophylactic programs.[1,2] In addition, pneumococci may become resistant to penicillin-type antibiotics, and other bacteria associated with OPSI are not sensitive to these drugs. Because cases of OPSI involving pneumococcal infection have been reported in patients who received both vaccination and penicillin prophylaxis, the use of prophylactic measures should never be allowed to result in a false sense of complacency.[32,33]

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Gastrointestinal Complications of Nonsteroidal Anti-inflammatory Drugs

RICHARD R. BABB, MD, *Palo Alto, California*

Nonsteroidal anti-inflammatory drugs have become increasingly popular, with more than 90 million prescriptions being written annually. These drugs inhibit the intracellular cyclooxygenase enzyme system, thus blocking the production of various prostaglandin compounds. This, in turn, interferes with normal mucosal protective mechanisms, leading to local injury. Gastrointestinal complications of nonsteroidal anti-inflammatory drug use include ulcerations, hemorrhage, perforation, stricture formation, and the exacerbation of inflammatory bowel disease. Treatment involves stopping the drug if at all possible and then instituting more specific therapy depending on the anatomic area that has been injured.

(Babb RR: Gastrointestinal complications of nonsteroidal anti-inflammatory drugs. West J Med 1992 Oct; 157:444-447)

. . . [T]here is now an overwhelming number of effective therapeutic agents. Nevertheless, everything has its price, and it is becoming more and more evident that these bonanzas are not pure gold.

MAXWELL WINTROBE, MD[1(p107)]

Almost 30 years ago, nonsteroidal anti-inflammatory drugs (NSAIDs) were first marketed in this country for the treatment of arthritis. More than a dozen NSAIDs (Table 1) are currently available for patient use, and it has been estimated that 90 million prescriptions are written annually.[2] As might be expected, an increasing number of side effects associated with their use have been reported,[3] the most common being gastrointestinal. In this article I will review possible and serious complications of NSAID therapy on the gastrointestinal tract (Table 2).*

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are popular by virtue of their analgesic, anti-inflammatory, antipyretic, and platelet inhibitory actions. These drugs block both the intracellular cyclooxygenase and lipoxygenase enzyme systems, which interferes with the normal inflammatory response and decreases the production of various prostaglandin compounds.[3,4] Each NSAID has its own pharmacodynamic characteristics, and patients' responses to each drug may vary greatly.

Gastrointestinal Complications

Esophagus

Little has been reported on the effect of NSAIDs on the esophagus. Two studies from Great Britain found a higher incidence of esophageal strictures in patients taking NSAIDs than in a control group: 49% versus 12% in one, and 31% versus 14% in the other.[5,6] Both groups analyzed were patients aged 65 and older, and most had a long history of reflux symptoms.

More recently Arnold and co-workers performed endoscopy on 50 patients who had taken indomethacin for at least a year.[7] Of these, 10 (20%) had erythema, erosions, or ulcers in the esophageal mucosa.

*See also "Nonsteroidal Anti-inflammatory Drugs and Ulcers," by Andrew H Soll, MD, on pages 465-468 of this issue.

Stomach and Duodenum

It is now clear that NSAIDs can damage the gastroduodenal mucosa, with serious sequelae including erosions and ulcers, hemorrhage, and acute perforation. The mucosa of the normal stomach is protected from noxious agents (cytoprotection) by numerous "defensive" mechanisms including the secretion of mucus and bicarbonate, mucosal blood flow, local production of prostaglandins, and rapid cellular repair.[8,9] By decreasing the local cellular production of prostaglandins, NSAIDs cause a disruption of these protective measures. There is subsequent increased permeability to acid and pepsin within the damaged mucosal cell, and erosions and ulcers may result.[9]

The association of NSAID use and ulcer disease is evident from numerous studies.[10-18] There are different ways to express this. In a review of eight articles surveying patients on long-term NSAID therapy, McCarthy noted a 46-fold greater chance of gastric ulcer and 8-fold increase for duodenal ulcer when compared with the normal population.[19] Kurata reviewed cross-sectional, case-controlled, and cohort studies and found an increased risk for NSAID gastric damage in all.[9] At any given time, the chance of a patient on NSAID therapy having a gastric ulcer has been estimated at 10% to 20% and a duodenal ulcer at 2% to 5%.[16] Pincus and Griffin estimate the relative risk of "adverse gastrointestinal effects" of NSAID therapy at 3:1 to 5:1.[20] Hospital admission rates have been found to increase by a factor of 4 to 5 in patients treated with NSAIDs compared with nonusers in two large studies.[17,21] About 20% to 40% of patients admitted to the hospital with acute upper gastrointestinal bleeding have been ingesting NSAIDs.[11,18,22]

Many patients taking NSAIDs will complain of dyspepsia, abdominal pain, or both. The correlation with objective findings of ulcer disease at endoscopy may be poor. Endoscopic evaluation has shown gastric mucosal hemorrhages, erosions, or ulcerations in 30% to 75% and duodenal lesions in as many as 26%.[15,23] Evidence of mucosal injury may occur within weeks to a few months of starting NSAID therapy.[16,18,19] Serious complications of ulcer disease such as hemorrhage and perforation may occur without warning with disastrous consequences.[12,14]

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TABLE 1.—*Nonsteroidal Anti-inflammatory Drugs*

Generic	*Brand Name (Manufacturer)*
Diclofenac sodium	Voltaren (Ciba-Geigy Corporation)
Diflunisal	Dolobid (Merck & Company)
Etodolac	Lodine (Wyeth-Ayerst Laboratories)
Fenoprofen calcium	Nalfon (Eli Lilly and Company)
Flurbiprofen	Ansaid (The Upjohn Company)
Ibuprofen	Motrin (The Upjohn Company), Advil (Whitehall Laboratories), Nuprin (Bristol-Myers Squibb)*
Indomethacin	Indocin (Merck & Company)
Ketoprofen	Orudis (Wyeth-Ayerst Laboratories)
Ketorolac tromethamine	Toradol (Syntex Laboratories, Inc)
Meclofenamate sodium	Meclomen (Parke-Davis Pharmaceutical Research)
Mefenamic acid	Ponstel (Parke-Davis Pharmaceutical Research)
Naproxen	Naprosyn (Syntex Laboratories, Inc)
Phenylbutazone	Butazolidin (Ciba-Geigy Corporation)
Piroxicam	Feldene (Pfizer, Inc)
Sulindac	Clinoril (Merck & Company)
Tolmetin sodium	Tolectin (McNeil Consumer Products Company)

*These are just some of the brands of this drug. The listing of these drugs in no way implies endorsement by either the author or THE WESTERN JOURNAL OF MEDICINE.

Small Intestine

In a series of experiments using radiopharmaceutical absorption tests, Bjarnason and associates have demonstrated NSAID-induced injury in the distal small bowel.[24-26] Volunteers and arthritis patients taking NSAIDs have been given nuclear-tagged compounds such as ethylenediaminetetraacetate labeled with chromium 51 to demonstrate intestinal permeability, leukocytes labeled with indium 111 for inflammation, erythrocytes labeled with technetium 99m for blood loss, ^{51}Cr-labeled proteins for protein loss, and taurohomocholic acid labeled with selenium 75 for bile salt absorption.[27] The scintigrams have shown evidence of increased small intestine permeability, ileal inflammation, blood loss, protein-losing enteropathy, and bile salt malabsorption due to NSAID ingestion. Arthritis patients not taking NSAIDs were studied in the same manner and showed no signs of distal small bowel inflammation. Evidence of small intestine mucosal injury persisted for as long as 16 months after NSAIDs were stopped. At 18 months, the test results were back to normal.[26]

Bjarnason and associates postulate that NSAIDs reduce the local cellular production of prostaglandin leading to increased mucosal permeability. This in turn allows luminal substances and bacteria to damage the mucosa, resulting in the adverse secondary effects.[27]

Occasional clinical reports have linked NSAIDs to small bowel disease. In 1966 five patients were noted to have small bowel ulceration, two of whom had been taking indomethacin for more than three months and had ulcers in the ileum.[28] Neoptolemos and Locke reported the case of an elderly patient taking phenylbutazone (Butazolidin) for three years who was operated on for small bowel obstruction and found to have six ileal ulcers.[29] Madhok and co-workers operated on three patients taking NSAIDs who had ileal ulcers.[30] All had ileal resections and the cessation of further NSAID therapy—over a 12- to 24-month follow-up, they remained well. Microscopic examination showed superficial ulceration and nonspecific inflammation. There were no signs of vasculitis or inflammatory bowel disease. Langman and colleagues retrospectively reviewed the records of 107 patients admitted to hospital with small or large bowel perforations, 28 (26%) of whom had been on NSAID therapy as compared with 13 (12%) matched controls.[31] Bjarnason and associates studied four patients with arthritis who had been taking NSAIDs 1.5 to 4 years.[32] All had extremely thin, concentric small bowel strictures that produced luminal narrowing and were occasionally missed on barium roentgenographic study. Finally, Morris and co-workers reviewed their small bowel enteroscopic findings on 15 arthritis patients taking NSAIDs.[33] All had iron deficiency anemia and normal roentgenograms and colonoscopy. Ten had mucosal lesions, including seven with erosions or ulcerations.

TABLE 2.—*Gastrointestinal Complications of Nonsteroidal Anti-inflammatory Drug Therapy*

- Esophageal
  - Esophagitis
  - Strictures
- Gastroduodenal
  - Erosions and ulcerations
  - Hemorrhage
  - Perforation
- Small bowel
  - Ileal inflammation
  - Strictures
  - Hemorrhage
  - Perforation
  - Protein-losing enteropathy
- Colon
  - Exacerbation of inflammatory bowel disease
  - Hemorrhage

Colon

There are several reports on the possible damage to colonic mucosa by NSAIDs. Rampton and associates found that 16 of 21 (76%) patients had taken a prostaglandin inhibitor before a relapse of ulcerative colitis, in contrast to 24 of 62 (39%) still in remission.[34] Rampton later noted case reports

wherein ulcerative colitis had developed in patients taking NSAIDs, the drug was stopped, the patients improved, and then they relapsed on resuming NSAID therapy.[35] Kaufman and Taubin described the cases of four patients—and another eight in a literature review—who had activation of both ulcerative colitis and Crohn's colitis after starting NSAID therapy.[36] In the same review, they noted an additional 20 patients without any antecedent history of inflammatory bowel disease in whom acute colitis developed after they began NSAID treatment.

Huber and colleagues reported the case of a patient in whom thin colonic strictures developed similar to those described in the small bowel after several years of NSAID (diclofenac) therapy.[37] The patient also had a history of anemia and ulcers in the ascending colon. Carson and coworkers described the cases of two patients with colonic bleeding due to ulcers in the right side of the colon, also during diclofenac treatment.[38]

Therapy

The treatment of gastrointestinal complications of NSAID therapy should be tailored to the specific circumstances of each patient. Certain risk factors for NSAID gastropathy have been identified: age older than 65, a history of ulcers, chronic illness, and receiving high doses of NSAIDs.[16,17,21] Moreover, therapy for injury to the gastroduodenal area differs from that to the small bowel or colon.

The therapy for NSAID gastropathy has been extensively reviewed.[19,39-42] Although numerous studies have been published, many are flawed by uneven experimental and statistical design, and important questions about management cannot yet be answered.[19] In summary, however, physicians should consider the following in patients with gastroduodenal (and presumably esophageal) injury:

- The NSAID should be stopped if at all possible. Perhaps other, nonulcerogenic drugs can be substituted for analgesia or joint inflammation.
- If an NSAID must be used, combinations with other NSAIDs[17,21] and corticosteroids[43] should be avoided. The lowest possible dose should be given because several studies suggest that doses higher than those recommended by the manufacturers are associated with an increased risk of gastrointestinal complications.[17,21]
- In patients with any of the risk factors for gastroduodenal injury noted earlier, physicians should be circumspect about the use of NSAIDs and even consider prophylactic ulcer therapy.
- The prevention of NSAID ulcerations remains controversial.[19,40,41] If a patient is elderly and has risk factors, misoprostol (Cytotec) can be used to prevent gastric ulcers. It may prevent duodenal ulcers also, but more data are needed on this point. This drug has not yet been proved effective in ulcer prophylaxis when a patient has a history of ulcer disease.[19] Histamine H_2-receptor antagonists such as ranitidine hydrochloride (Zantac) have been shown to prevent duodenal but not gastric ulcers.[19] The potential cost of prophylactic therapy using misoprostol is staggering, which adds to the debate about the wisdom of this approach.[2]
- If a patient taking NSAIDs has a history of peptic ulcer disease and other risk factors, or if an ulcer develops with NSAID therapy, full doses of antacids or H_2-receptor antagonists should be used.[19,42] If the ulcer is greater than 5 mm in diameter on endoscopy, such therapy may have to be extended for months before the ulcer is completely healed. Omeprazole surpassed ranitidine in the healing of NSAID-induced gastric ulcers and is an attractive alternative drug[44]; however, its use for this purpose has not been approved by the Food and Drug Administration. On the basis that misoprostol at a dose of 200 μg has an antisecretory effect similar to H_2-receptor antagonists, Graham has suggested the use of this synthetic prostaglandin in the treatment of NSAID ulcers.[41]
- Once NSAID ulcers are healed, guidelines for maintenance therapy to prevent recurrence are not available. Candidate drugs include H_2-receptor antagonists, omeprazole, and even misoprostol, but a definite answer on the basis of existing information is not possible.[19,41]

Patients with NSAID damage to the small bowel or colon should stop the drug if at all possible. It has been shown recently that the use of metronidazole (Flagyl) and sulfasalazine (Azulfidine) reduces signs of inflammation in NSAID enteropathy.[45,46] Whether or not these drugs will be helpful clinically remains to be investigated. Surgical intervention may be required for obstructive symptoms due to strictures or profound bleeding.

Conclusion

The most common side effect of NSAID therapy relates to gastrointestinal damage. A wide variety of disorders may develop in patients taking NSAIDs, ranging from minor dyspepsia to life-threatening ulcer bleeding or perforation. Although NSAID gastropathy has been the complication most evaluated, other parts of the gastrointestinal tract including the esophagus, small bowel, and colon may be seriously injured, leading to mucosal inflammation, hemorrhage, and obstruction due to strictures. Nonsteroidal anti-inflammatory drug therapy may cause a serious relapse of inflammatory bowel disease. Treatment depends on the clinical situation and anatomic area involved.

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Epitomes

Important Advances in Clinical Medicine

Ophthalmology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in ophthalmology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Medical Treatment of Retinal Infections in Patients With AIDS

CYTOMEGALOVIRUS (CMV) retinopathy and other retinal infections are among the most feared complications of the acquired immunodeficiency syndrome (AIDS). There are now two drugs approved by the Food and Drug Administration for the treatment of CMV retinopathy: ganciclovir sodium and foscarnet. Both are administered intravenously in a similar manner. Initially patients are given an "induction" course of high doses to suppress infection, followed by a life-long "maintenance" regimen to prevent disease reactivation and progression, as neither drug eliminates virus from the eye. The safety and efficacy of these drugs were recently compared in a multicenter clinical trial sponsored by the National Institutes of Health. There were no differences in major ophthalmic end points such as final visual acuity, but the protocol was suspended early when it was determined that patients treated with foscarnet survived several months longer than patients treated with ganciclovir. The cause for the differential survival rates could not be determined. Although this finding could possibly be related to the drugs themselves, it could also have been related to other, uncontrolled factors, such as a differential use of antiretroviral drugs. Both drugs have serious systemic side effects; ganciclovir is a bone marrow suppressant, and foscarnet causes renal damage. Despite the increased survival associated with the use of foscarnet, patients did not tolerate it as well as ganciclovir. Because both drugs protect against loss of vision, patients and their primary care providers should participate in the decision for choosing which drug to use, based on nonophthalmic factors such as cost (foscarnet is more expensive currently than ganciclovir), tolerance, the risk of side effects, and perceived survival benefit.

After ganciclovir became available, the intravitreal administration of the drug was studied as an alternative route for patients with drug-induced neutropenia. Interest in intravitreal ganciclovir has waned for several reasons: Neutropenia can now be treated with the concurrent use of leukocyte growth factors sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) and filgrastim (granulocyte colony-stimulating factor [G-CSF]); patients can be switched from ganciclovir to foscarnet or vice versa as toxic reactions develop. Intravitreal injections have their own associated risks, such as vitreous hemorrhage and bacterial endophthalmitis. This therapy is now usually reserved for patients who cannot tolerate any parenteral drug.

In addition to CMV retinopathy, there are other, less common but equally serious, human immunodeficiency virus-related retinal infections. At least a dozen pathogens have been reported, but varicella-zoster virus (VZV) retinitis and ocular toxoplasmosis are the most common. Varicella-zoster virus retinitis is a rapidly progressive necrotizing infection, and patients should be treated immediately with high-dose intravenous acyclovir sodium; an initial ten-day course is usually recommended. A decision to continue therapy with either intravenous or oral acyclovir is currently based on the patient's response to treatment and the appearance of retinal lesions. The need for long-term maintenance therapy to prevent recurrent VZV retinitis is a subject of controversy. Because many patients are left with poor vision despite treatment, the concurrent use of several intravenous antiviral drugs is being investigated.

Ocular toxoplasmosis is treated with a combination of pyrimethamine and sulfadiazine or clindamycin. Although retinal lesions respond well to this treatment, they can reactivate unless patients are maintained on continuous low-dose therapy with at least one drug. Clindamycin is used most commonly for this purpose because of pyrimethamine-associated bone marrow suppression and the frequency of allergic reactions to sulfonamides in AIDS patients. Several new drugs are also under study for the treatment of *Toxoplasma gondii* infections.

Unfortunately, serologic tests cannot confirm these diagnoses because of the high prevalence of antibodies to CMV, VZV, and *T gondii* in the general population, and retinal biopsies are too risky for diagnostic use in most situations. Ophthalmologists distinguish among them on the basis of subtle differences in lesion appearance, distribution, course, and inflammatory signs. Primary care providers should suspect infections other than CMV retinopathy if an eye becomes red and painful; CMV infection does not cause sufficient inflammation to produce those signs, but toxoplasmosis, syphilis, and fungal infections can.

Because retinal tissue destroyed by infection cannot be regenerated, visual results depend on early diagnosis. Patients should be encouraged to seek immediate ophthalmologic evaluation if they have blurring, visual field defects (blind spots), or multiple floating spots before one or both eyes. With accurate diagnosis and aggressive therapy, many AIDS-related retinal infections can be controlled. Therapies continue to evolve as new drugs become available and effective treatment regimens are identified.

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Photorefractive Keratectomy

PHOTOREFRACTIVE KERATECTOMY is a surgical procedure to correct nearsightedness (myopia), farsightedness (hyperopia), and astigmatism. The procedure involves recontouring the anterior surface of the cornea with an excimer laser that uses ultraviolet light (193 nm). Each laser pulse ablates 0.2 to 0.3 μm of corneal tissue, with almost no thermal or other injury produced in the immediately adjacent tissue. The anterior cornea is reshaped by ablating small amounts of tissue from the corneal surface; to flatten the cornea, more tissue is removed centrally than is removed from the periphery, and corneal steepening is achieved by removing little or no tissue centrally and progressively more tissue towards the corneal periphery. The end result is that a central round area of the cornea measuring between 4 and 6 mm in diameter and overlying the pupil is treated, with a maximum depth of ablation of about 10% of corneal thickness. Clinical trials of photorefractive keratectomy are under way in the United States at about 30 centers, and the Food and Drug Administration (FDA) is carefully controlling the number of patients enrolled in these studies. The FDA has determined that five-year follow-up will be evaluated before deciding whether or not to approve this procedure for the correction of refractive errors in otherwise healthy eyes. In Europe, Canada, and Asia, where governmental regulation is less restrictive, many lasers are in place and more than 10,000 eyes have been treated.

Data from the clinical sites in the United States and reports from abroad show that, in the short run, the procedure appears to be reasonably safe and effective for the correction of low-to-moderate myopias. Beyond 6 diopters, partial or even total regression of the effect is common, resulting in poor predictability of ultimate results. Because 90% of nearsighted Americans have refractive errors of 5 D or less, most patients are candidates who could expect a favorable result if they need any correction beyond spectacles or contact lenses. Clinical follow-up on a large number of patients has been limited to about two years, so long-term safety and stability remain to be determined. In the short term, a superficial corneal haze is typical after the procedure, but this generally decreases in intensity over time. A few patients have measurable decreases in visual acuity or contrast sensitivity for several weeks after the operation; a persistent decrease in visual acuity due to substantial corneal haze occurred in about 2% of patients in one center in Europe. Although most treatments have been performed for myopia, recent studies suggest this laser can be effective also for the treatment of astigmatism.

Photorefractive keratectomy is to be distinguished from radial keratotomy, a procedure that has been done in the United States since 1978 to correct nearsightedness and astigmatism. Radial keratotomy involves creating incisions deep (90% depth or greater) into the corneal stroma. Four, eight, or more incisions are created, starting in the paracentral cornea and extending radially to the corneal periphery. A large multicenter National Eye Institute-sponsored clinical trial, the Prospective Evaluation of Radial Keratotomy (PERK) Study, was carried out in the early and mid-1980s to define the safety and effectiveness of this procedure. Vision-threatening complications are rare after radial keratotomy, but predictability is somewhat limited; about two thirds of the patients in the PERK study had adequate vision without spectacles or contact lenses after the operation.

In addition to correcting refractive error, the excimer laser is also being used, as an alternative to corneal transplantation, to remove anterior corneal opacities. This procedure, called phototherapeutic keratectomy, has been largely successful to date, and the FDA is currently considering granting approval of the laser for this indication. Should approval be granted, this procedure will provide an outpatient, cost-saving surgical alternative to about 10% of the 40,000 patients who undergo corneal transplant each year in the United States.

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Macular Surgery

THE APPLICATION OF vitreoretinal microsurgical techniques to disorders of the macula, the central retinal visual area, has become one of the most exciting and rapidly developing areas in ophthalmology. Until recently the primary indication for a macular operation has been the treatment of avascular membranes that may develop on the surface of the macula, descriptively termed "macular pucker." Since the late 1970s the surgical removal of epimacular membranes has improved the vision in about 80% of patients.

The development of idiopathic full-thickness macular holes is a common cause of central vision loss, typically affecting older women, and occurring in both eyes in 10% to 20% of patients. A new hypothesis implicated centrifugal traction of the vitreous parallel to the retinal surface at the vitreomacular interface (tangential traction) in the pathogenesis of idiopathic full-thickness macular holes. This prompted the report that the surgical treatment of macular holes has met with stunning yet widely corroborated success.

Previously considered to have an irreparable condition, 42% of patients had improvement in their vision, with 19% returning to near-normal visual function. Continuing refinements in surgical techniques suggest that substantially better success rates may be expected. Surgical prophylaxis for impending macular holes, when visual symptoms and clinical signs may be subtle yet reversible, is the subject of an ongoing multicenter, prospective clinical trial.

Successful macular hole operations have cast doubt on previous concepts of vitreomacular pathophysiology based on clinical evaluation. Detachment of the vitreous from the surface of the macula is a common and typically benign age-related event. It is now recognized, however, that the exact relationship of the posterior vitreous to the macula can often be determined only at the time of surgical intervention. The most careful preoperative evaluation has frequently been found at the time of a macular operation to be misleading and unreliable, either not recognizing or underestimating the role of the vitreous in the pathologic process. Other disorders, such as loss of vision due to anteroposterior vitreomacular traction caused by incomplete vitreous detachment from the macula, have been recognized and shown to be responsive to surgical intervention. Indeed, it is increasingly appreciated that macular pucker, as well as tangential and anteroposterior vitreomacular traction, may occur alone or in concert, even superimposed on other macular disease, causing or contributing to loss of central vision that may be amenable to surgical intervention.

The development of neovascular membranes beneath the macula is an important cause of central vision loss in a multitude of disorders, particularly the presumed ocular histoplasmosis syndrome and, more commonly, age-related macular degeneration. Recently the surgical removal of submacular neovascular membranes complicating presumed ocular histoplasmosis syndrome and age-related macular degeneration has been reported with encouraging, occasionally remarkable, results. Such developments have ushered in a new era in vitreoretinal surgical treatment by revolutionizing our understanding of clinical vitreomacular pathophysiology and expanding the application of current microsurgical techniques to macular diseases until only recently unrecognized, misunderstood, or considered irreparable.

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Laser Treatment of Diabetic Retinopathy

DIABETES MELLITUS is the leading cause of blindness in working-age Americans and accounts for 8,000 cases of new blindness each year in the United States. "Diabetes 2000" is an ambitious, long-term education project of the American Academy of Ophthalmology, designed to eliminate preventable blindness from cases of diabetes by the year 2000. Ophthalmologists and primary care physicians must share advances to accomplish this goal.

Two distinct forms of diabetes mellitus are recognized—juvenile onset (type I) and adult onset (type II). Furthermore, two distinct forms of diabetic retinopathy that may cause blindness occur—proliferative diabetic retinopathy and diabetic macular edema. Proliferative diabetic retinopathy consists of neovascular tissue that grows on the surface of the retina and into the vitreous cavity. If untreated, bleeding occurs into the vitreous, which then contracts, sometimes resulting in retinal detachment. Diabetic macular edema is caused by incompetent vessels leaking serum and lipid into a poorly perfused central retina. As retinal thickening occurs, photoreceptor function decreases and central vision is compromised. Juvenile-onset diabetes carries a higher risk of severe proliferative retinopathy, but because there are more cases of adult-onset diabetes, the latter group comprises a significant proportion of patients with blindness. In many instances, blindness from diabetes can be prevented by early detection and prompt photocoagulation treatment.

In 1976 a National Eye Institute (NEI)-funded Diabetic Retinopathy Study showed that panretinal scatter photocoagulation reduced the rate of profound loss of vision from severe proliferative diabetic retinopathy by 50%. Results are lasting: Of high-risk patients who had a favorable response to photocoagulation, 80% maintained 20/40 (reading) vision five years after treatment. The effects of photocoagulation on the management of less severe stages of diabetic retinopathy were not known until recently. A second NEI clinical trial showed that early treatment, when compared with observation only, was associated with a small reduction in the incidence of severe vision loss, but five-year rates of loss of vision were low in both the early treatment and observation groups. Therefore, if careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate nonproliferative diabetic retinopathy. When retinopathy is more severe, scatter photocoagulation should be considered and should not be delayed if the eye has reached the high-risk proliferative stage.

Diabetic macular edema is a more common cause of severe loss of vision than proliferative diabetic retinopathy. For eyes with macular edema, focal macular photocoagulation is the only effective treatment that reduces the risk of moderate visual loss. Treatment should be considered only for eyes with clinically significant macular edema, such as edema that involves or threatens the center of the macula. Focal treatment stabilizes visual acuity, increases the chance of visual improvement, decreases the rate of subsequent loss of vision by decreasing the frequency of persistent macular edema, and causes only minor visual field loss. Timing is therefore important. Treatment should ideally be applied before serious vision loss occurs.

Photocoagulation has been proved to be cost effective. A computer-simulation model was designed to predict the economic effects of the treatment of diabetic retinopathy in juvenile diabetes. Using treatment recommendations provided by these clinical trials, the model predicted a cost savings of $9,571 per year for each new patient diagnosed and appropriately treated. If all patients with diabetes mellitus received appropriate care, the predicted annual savings would exceed $167 million and 79,236 person-years of sight. Unfortunately, it is estimated that 22% of patients with type I diabetes and 40% of those with type II diabetes are not obtaining

appropriate eye care. It is less expensive to provide preventive care than to support subsequent disability and its associated personal and social suffering.

Using the results of these clinical trials, a treatment plan for diabetic retinopathy has been designed and proved medically and cost effectively. The trials have shown that most patients with diabetes go blind because they are treated too late. They must be evaluated early to reap the benefits of these studies.

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Retinitis Pigmentosa—New Advances in Ophthalmic Genetics

RETINITIS PIGMENTOSA is both clinically and genetically heterogeneous. It comprises a group of X-linked autosomal recessive and autosomal dominant diseases that affect 50,000 to 100,000 people in the United States, with the incidence ranging from 1 in 3,000 to 1 in 7,000. The early symptoms of retinitis pigmentosa include night blindness and a loss of peripheral fields of vision. As the condition progresses, visual acuity and central vision are also affected. Examination of the fundus reveals attenuated retinal vessels, bone-spicule pigment around the periphery of the retina, and occasionally pale optic discs.

Molecular biologic studies have defined the genetic defects for at least some of the persons and families who have autosomal-dominant retinitis pigmentosa. Most of the mutations discovered to date are the result of changes in a single nucleotide in the rhodopsin gene. Different families may carry different mutations, but affected members of the same family carry the same dominantly inherited mutation. These mutations lead to single amino acid changes in the rhodopsin molecule. The first mutation discovered was a C-to-A base change in the 23rd codon of the rhodopsin gene that resulted in a substitution in the 23rd amino acid of histidine for proline. This mutation was denoted as the proline-23-histidine mutation. In a recent report of 161 unrelated patients with autosomal-dominant retinitis pigmentosa who were screened, 26 (24%) were found to carry a point mutation in the rhodopsin gene. This study described 13 different mutations at 12 different amino acid positions. Research is under way to uncover the molecular defects in the rest of these patients by exploring the possibility of defects in other retinal and photoreceptor genes, such as arrestin (also known as S antigen), transducin, peripherin, and others.

Many investigators have attempted to correlate observed genetic heterogeneity with variability in the clinical severity and prognosis of autosomal-dominant retinitis pigmentosa. Initial observations suggested that patients with certain mutations, such as proline-23-histidine, threonine-58-arginine, glycine-182-serine, and threonine-17-methionine, may have better long-term prognoses than others for the retention of good visual acuity and functional peripheral visual fields. In patients with the proline-347-leucine mutation, there is an increased likelihood of more severe functional impairment. The age of onset and severity of the disease, however, may vary substantially among patients with the same mutation.

How can these new discoveries be used to diagnose and treat patients with retinitis pigmentosa? Molecular genetics, in conjunction with a review of family history and careful clinical examination, can in some cases determine whether a person with a family history of autosomal-dominant retinitis pigmentosa is carrying the disease gene while asymptomatic. This information can assist persons in making career and family choices. The application of further clinical and basic research will one day help to decipher the biochemical basis for retinal degeneration in retinitis pigmentosa, which we hope will lead to a rational basis for treating the disorder. Further research is also required to determine the molecular defect in the great majority of persons with dominantly inherited retinitis pigmentosa, as well as in patients with the autosomal recessive and X-linked type. Patients with this disorder optimally should be referred to centers with experience in its diagnosis and treatment and be enrolled in clinical studies.

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Current Therapy for Disorders of the Optic Nerve

OPTIC NEURITIS is characterized by subacute unilateral loss of central vision in patients younger than 40 years, associated with pain on eye movement, diminished pupillary response, and optic disc edema in about 40%. It may be associated with systemic disorders such as systemic lupus erythematosus and syphilis and may be mimicked by parasellar tumors. Most cases are idiopathic, in which there may be a strong association with multiple sclerosis. The value of corticosteroid therapy in idiopathic optic neuritis has not been proved. Early reports indicated that treatment reduced pain and increased the speed of visual recovery but did not appreciably affect the final level of visual acuity. Most neuro-ophthalmologists have treated only those patients with severe pain or with a definitive need for the rapid recovery of vision, such as patients with severe loss of vision, or only one functional eye. The recent national multicenter clinical trial of systemic corticosteroid use in optic neuritis (Optic Neuritis Treatment Trial) showed that oral prednisone therapy alone had no beneficial effect and was associated with an increased risk of recurrence; study investigators have therefore recommended against its use. An initial course of intravenous methylprednisolone sodium succinate, however, followed by oral prednisone was beneficial in patients with visual acuity worse

than 20/40. In patients with more severe vision loss, consideration should be given to this therapy.

Nonarteritic anterior ischemic optic neuropathy, an infarct of the optic nerve head, is the most common cause of acute optic neuropathy in patients older than 50. It presents as acute, painless, unilateral loss of vision associated with impaired pupillary response and optic disc swelling. It typically occurs as a single episode but may progress over a period of weeks in 20% to 30% of cases. Recent studies suggest that optic nerve sheath decompression, a surgical procedure in which cerebrospinal fluid is released through an incision into the subarachnoid space surrounding the optic nerve, may reduce permanent optic nerve damage in the progressive form of nonarteritic anterior ischemic optic neuropathy. The procedure, which theoretically works by reducing intrasheath pressure, allowing for improved blood flow to the optic nerve head, has proved effective in chronic optic disc edema from increased intracranial pressure (most commonly pseudotumor cerebri). Its use in nonarteritic anterior ischemic optic neuropathy, however, is controversial. A recent series of reports indicated notably improved vision after optic nerve sheath decompression in a high percentage of patients, but several investigators have presented data that do not corroborate this success. A multicenter clinical trial, the Ischemic Optic Neuropathy Decompression Trial, has recently been funded by the National Eye Institute to evaluate the effectiveness of this therapy; recruitment of some 300 patients over 18 months was started in 1992.

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Graves' Ophthalmopathy

THE DIAGNOSIS OF Graves' ophthalmopathy is purely clinical and is unrelated to the systemic thyroid state. Although most patients have hyperthyroidism, euthyroid patients or those with hypothyroidism also present with ocular symptoms. Orbital computed tomographic scans are helpful in predicting possible loss of vision but are rarely necessary for the diagnosis of Graves' ophthalmopathy. Although some form of symptomatic ocular involvement is present in at least 31% of patients with Graves' thyroid disease, the ophthalmopathy may occur, both in timing and severity, independent of the thyroid disease.

Data on the natural history of Graves' ophthalmopathy remain scarce. Most investigators agree that the disease is self-limiting and runs a course of exacerbations and spontaneous remissions, becoming stable within 18 to 36 months. Hence, ongoing collaboration among primary care physicians, endocrinologists, and ophthalmologists is paramount for optimal patient care.

There is no known effective treatment to prevent the development of Graves' ophthalmopathy. Our efforts remain directed at palliating symptoms. Managing the thyroid dysfunction in these patients is the first logical step in the treatment of Graves' ophthalmopathy, but the disorder may continue to progress.

When considering treatment, patients can be divided into three major categories: those with active vision-threatening optic neuropathy, those with active nonvision-threatening ophthalmopathy, and those with chronic stable ophthalmopathy. Patients with acute Graves' optic neuropathy require urgent treatment to prevent permanent loss of vision. The longer treatment is delayed, the less adequate visual recovery will be. Corticosteroid therapy is generally the first line of treatment. In patients who cannot tolerate corticosteroids, cyclosporine has been recently suggested as an alternative or adjunct to corticosteroids, but its effects on ophthalmopathy are not well documented and the side effects are potentially serious. For patients who have a recurrence of optic neuropathy with tapering of their corticosteroid regimen or for those who do not respond to or simply cannot tolerate corticosteroid therapy, either orbital decompression or orbital irradiation is indicated. Orbital decompression remains a successful treatment of optic neuropathy, whereas orbital radiotherapy remains controversial because of the risks of dry eye and radiation retinopathy associated with low-dose irradiation. In addition, the risk of inducing tumors is unknown.

For patients with nonvision-threatening acute ophthalmopathy, symptomatic treatment and expectant follow-up are indicated. Artificial tears, lubricants, night-time patching of the eyelids, elevation of the head of the bed, and wrap-around glasses are helpful treatments. No controlled trials have been done that demonstrate the efficacy of corticosteroid therapy or irradiation in altering the natural history of the ophthalmopathy or in improving proptosis or diplopia once the disease has become stable. The risk of corticosteroid use or irradiation must therefore be weighed against the short-term improvement in active inflammation. If steroids are prescribed, they should be given over a course of two to three weeks, with rapid tapering to avoid prolonged treatment even if inflammation recurs.

Once fibrosis has developed in patients with chronic stable thyroid ophthalmopathy, neither corticosteroid nor radiation therapy has a role because active inflammation is not present. For these patients, surgical reconstruction may be considered. Most surgeons agree that the reconstructive operations should be done in sequence with orbital decompression, followed by the correction of double vision, and, finally, an eyelid operation. The surgical procedure must be tailored to the special needs of each patient. Cosmetic orbital decompression in the absence of functional diplopia must be undertaken with caution because diplopia will develop in 30% to 50% of patients after surgical decompression.

An often overlooked yet equally important component of Graves' disease is the psychosocial stress associated with the disease. Graves' disease often has substantial economic and social effects, as patients are commonly in their wage-earning years and, in some cases, are unable to do their jobs because of their visual symptoms. The cosmetic disfigurement produced by ophthalmopathy may cause a reactive depression, placing stress on the family. These patients may be referred to a support group through the National Graves' Disease Foundation (11111-2A San Jose Blvd, Suite 123, Jacksonville, FL 32223).

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Small-Incision Cataract Operation

CATARACT EXTRACTION with intraocular lens implantation is currently the most common surgical procedure in the United States. In the past 20 years a revolution has occurred in the techniques and technology of cataract operations. With the earlier "intracapsular" technique, the lens and capsule were removed intact through a large (10 to 14 mm) incision at the edge of the cornea. This large incision required more suturing to close, was more traumatic to the eye, and often resulted in postoperative astigmatism. When studies showed that leaving the posterior lens capsule intact would reduce the risk of postoperative macular edema and retinal detachment, most surgeons adapted an "extracapsular" technique wherein the anterior lens capsule was opened and the lens nucleus manipulated forward and removed from the eye through a large incision.

The introduction of phacoemulsification in the 1970s began a sequence of innovations that made small-incision operations possible in the late 1980s. Phacoemulsification is the process of concentrating ultrasonic energy through a handpiece to the lens nucleus. The nucleus is fragmented into fine particles that are aspirated from the eye. The lens can be removed entirely through a 3-mm incision. To implant an intraocular lens in the eye, however, the wound still had to be extended to 6 to 7 mm.

Other innovations soon followed. Viscoelastic agents provided a clear, viscous material that could coat and protect the corneal endothelium from the ultrasonic energy, making the cataract operation safer for the cornea. These agents also helped maintain the shape of the anterior chamber and allowed for excellent visibility during procedures. Capsulorhexis, a technique for making a controlled round or oval tear in the anterior capsule, preserved the strength and elasticity of the remaining lens capsule. This technique made phacoemulsification safer and intraocular lens placement more consistent. New methods of dissecting the lens nucleus and separating the layers of lens cortext using cannulas and irrigation were introduced, which allowed easier access to the nucleus and a greater margin of safety during phacoemulsification. Intraocular lens designs were tailored for smaller incisions. Lenses were designed to fit through a 5-mm incision; foldable silicone lenses capable of insertion through a 4-mm incision were also introduced. Wound designs were devised that are self-sealing, making "single-stitch" and "no-stitch" operations possible.

Small-incision techniques are being adapted by a growing percentage of ophthalmologists. Recent studies have shown that the main advantages of small-incision cataract operations are less trauma to ocular tissues, less immediate postoperative inflammation, less postoperative astigmatism, and more rapid visual rehabilitation.

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Alerts, Notices, and Case Reports

Maternal Death Due to Rupture of a Low Transverse Cesarean Section Incision During Labor at Home

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VAGINAL BIRTH AFTER cesarean section has been shown in numerous large series of cases to have statistical benefit outweighing risk.[1] Women with a single previous low-transverse cesarean section, a clinically normal pelvis, and no obstetric contraindication to vaginal delivery are commonly offered a trial of labor. Undetected ("silent") dehiscence of the uterine scar occurs in 0.5% to 2% of cases of vaginal delivery after a cesarean, but fortunately serious complications such as placenta accreta or outright uterine rupture are rare.[2,3] In the largest single-institution experience published,[4] among 7,598 patients attempting vaginal delivery after a cesarean, there were 54 cases of scar dehiscence and 61 of clinically unmistakable uterine rupture, with 2 fetal deaths and 1 maternal death. There were 14 emergency hysterectomies done because of uterine rupture. Life-threatening emergencies occur in about 1% of women attempting vaginal birth after cesarean section, requiring vigilance during labor and the capability for rapid intervention.

Report of a Case

The patient, who was gravida 8, para 3, aborta 4, desired vaginal delivery after a previous cesarean section. She had had an uneventful term vaginal delivery during her first pregnancy. The second labor was complicated by umbilical cord prolapse, and delivery was by a (documented) low-transverse cesarean section. During the third pregnancy, she expressed a desire for a trial of labor and had an uncomplicated vaginal delivery.

The final pregnancy was marked by three changes of physicians and by frequently missed appointments. During the late third trimester, a trial of labor was discussed. The patient indicated that she desired to stay at home until in established active labor and had engaged a "birthing coach" to check heart tones and do cervical examinations at home. The potential danger to mother and baby of such an approach was explained, and the patient agreed to come to the hospital for evaluation at the start of regular uterine activity.

At 40 weeks' gestation, the cervix was long and closed and the presenting vertex high. At 41 weeks, the cervix was unchanged and the fetus was in breech presentation, with an estimated fetal weight of 4,424 grams. A cesarean section was recommended and accepted. The patient was admitted to the hospital but left 30 minutes before the scheduled procedure. She was reached by telephone the next day and the cesarean section was rescheduled, but she did not return to the hospital. She was again contacted and expressed a desire for a "second opinion." A copy of the prenatal record together with a written discussion of the risks of the situation were given to the patient. She phoned later that day to say that a second physician had examined her and found the fetus to be in vertex presentation and that she had decided to await the onset of labor. She refused to come in to the hospital for monitoring or for further evaluation.

The patient was found dead at home three days later. She had apparently been at home alone during labor. According to the coroner's report, she had been timing contractions, and these were recorded at four-minute intervals. At autopsy, the fetus was in vertex presentation. The uterus was ruptured along the previous low-transverse incision, with hemoperitoneum and extrusion of the fetal arm and leg into the peritoneal cavity. The cause of maternal and fetal death was maternal hemorrhage due to uterine rupture.

Discussion

A trial of labor after a single low-transverse cesarean section is successful in 60% to 80% of women.[1] Recognized risks of a previous cesarean section include silent dehiscence of the uterine scar, uterine rupture, and placenta accreta.[2] If, however, a trial of labor occurs in a hospital able to monitor the patient and fetus closely and to intervene rapidly for intrapartum complications, serious injury to mother or fetus is rare. In this situation, the risk-benefit considerations favor a trial of labor over another cesarean section.[3]

Despite the cumulative excellent safety record of attempted vaginal delivery after cesarean section, a trial of labor is not without risk. Two recent articles report a total of 20 cases of uterine rupture during trials of labor in the Salt Lake City, Utah, and Denver, Colorado, areas.[5,6] Catastrophic sequelae for fetus or neonate occurred in eight of these, but all of the women, including one who suffered uterine rupture during attempted vaginal birth at home, did survive. Scott commented on the "cavalier" attitude toward the history of a cesarean section that is expressed by some patients, some insurers, and some physicians.[5] In San Diego County, there are several lay midwives who will attend home deliveries for patients with previous cesarean sections. At least one free-standing birthing center staffed by certified nurse-midwives accepts patients who have had cesarean sections for delivery in a facility that has no capabilities for emergency intervention. For patients who desire a vaginal delivery but are advised against one, as in this case, there are local sources of misinformation that would label the physician as "knife happy" and minimize the risks of vaginal birth after a cesarean.

The patient in this report had come to think that vaginal delivery was safe and that cesarean section was dangerous. Because she had raised the issue of staying at home until active labor, she had been informed in unusual detail of the possible hazards but, despite this discussion and the large size of the baby, chose a course that led to her death.

(Catanzarite VA, Foster E, Robinette P, Cousins LM, Schneider JM: Maternal death due to rupture of a low transverse cesarean section incision during labor at home. West J Med 1992 Oct; 157:454-455)

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Uterine rupture is reported to occur in 0.2% to 0.8% of patients having a trial of labor after a previous cesarean section[1-4] and may occur early in labor.[6] Although uterine rupture commonly results in fetal distress, maternal death is rare if the event occurs in a hospital.[7] To prevent tragic consequences, patients planning to have vaginal delivery after cesarean section should be evaluated early in labor and monitored appropriately in a hospital capable of rapidly mobilizing for obstetric emergencies.

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Isolation of *Borrelia burgdorferi* From Ticks in Southern California

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SINCE ITS INITIAL DESCRIPTION in 1975, Lyme disease has been reported from 46 states, although the causative agent of Lyme disease, *Borrelia burgdorferi*, has not been as widely identified.[1] Three regions in the United States have accounted for the vast majority of cases: the northeastern United States (from Massachusetts to Maryland), the Midwest (Wisconsin and Minnesota), and the West (Oregon and northern California). Until early 1991, no cases of endemic Lyme disease were documented and *B burgdorferi* had not been isolated in southern California.

Borrelia burgdorferi Identification in Orange County

From 1984 through August 1991, the Vector Control District of Orange County captured and tested 328 *Ixodes pacificus* ticks, the vector of Lyme disease in California, for *B burgdorferi*. In February 1991, 31 *I pacificus* ticks were collected from a ravine in San Clemente, near the border with San Diego County. One tick was culture-positive for *B burgdorferi*. This organism grew in Kelly-Stoner-Barbour II medium and was confirmed as *B burgdorferi* by the California Department of Health Services (CDHS) Microbial Disease Laboratory. The identity was confirmed by immunofluorescent microscopy using monoclonal antibodies H5332 (directed against OspA) and H68 (directed against OspB), both of which are specific for *B burgdorferi*.* This was the first isolation of *B burgdorferi* from a tick in southern California.

(Meyers HB, Moore DF, Gellert G, et al: Isolation of *Borrelia burgdorferi* from ticks in southern California. West J Med 1992 Oct; 157:455-456)

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
EIA = enzyme immunoassay

Lyme Disease Reported in San Bernardino County

In April 1991 a case of possible Lyme disease meeting surveillance criteria was reported to the San Bernardino County Department of Public Health. The patient, a 55-year-old man, gave a history of a tick bite February 24, 1991, while hiking in Cucamonga Canyon in the San Gabriel Mountains (including an area known locally as "Tick Overlook"). The tick was removed from the lower left abdomen. An erythematous rash occurred on February 26 that eventually reached 8 cm in diameter. No fever, myalgia, or other symptoms were noted. The patient sought medical care the same day, and Lyme disease was diagnosed. A regimen of tetracycline, 500 mg four times a day for ten days, was prescribed. A serologic test on April 3 was negative (total antibody by enzyme immunoassay [EIA], 0.33; positive >0.80). On June 13 the patient was examined by another health care provider because of swelling and pain in the left knee. A second EIA was negative (0.29). The left knee symptoms subsided after five days.

The tick was identified as *Ixodes pacificus* by an entomologist with Vector Control in San Bernardino and by the CDHS Microbial Disease Laboratory. *Borrelia burgdorferi* was not cultured from this tick. This may have been a false-negative result due to the improper preservation of the tick. This case report, however, led to the trapping of ticks in the same vicinity in March 1991. Subsequent culture of these ticks was positive for *B burgdorferi* at the CDHS Microbial Disease Laboratory. This is the first positive identification of this organism from ticks in San Bernardino County.

Discussion

Lyme disease became legally reportable in California in April 1989. From April 1989 through April 1991, San Bernardino and Orange counties reported 14 and 12 cases, respectively. Of these, five cases from San Bernardino and two cases from Orange may have been locally acquired (no out-of-county travel histories). Only three cases presented with the characteristic lesion of erythema migrans, and in none of these patients was it possible to isolate the causative organism.

Ixodes pacificus, or the western black-legged tick, can be found in many areas of San Bernardino and Orange counties. The data presented here, however, show a low prevalence of *B burgdorferi* in ticks in Orange County. This rate is even

*Allen Barbour, MD, provided the monoclonal antibodies for confirming the identification of *Borrelia burgdorferi*.

lower than that reported in northern California (1% to 2% overall, Robert Murray, DrPH, CDHS, oral communication, April 1992). Both these rates are lower than those seen in the northeastern United States. These lower rates may be due to a difference in the host-parasite relationship. Immature stages of *I pacificus*, unlike those of *Ixodes dammini*, the northern deer tick of the northeastern and midwestern United States, feed on lizards and small mammals. This may play a role in reducing *B burgdorferi* transmission because it is thought that lizards do not sustain infection with *B burgdorferi*. For these reasons a Lyme disease incidence of a similar magnitude to that observed in the northeastern US is not expected in southern California.

Preventive measures for infection with *B burgdorferi* are based on avoiding tick contact. This includes avoiding grass and brush vegetation, wearing light-colored long-sleeved shirts and long pants tucked into socks or boots, applying a tick repellent to clothes, and doing frequent body checks for ticks. Ticks adhering to skin should be removed with forceps or tweezers using a gentle and steady pulling motion that avoids crushing the tick and releasing its bodily fluids. The tick may be kept alive by placing in a vial with a moist piece of cotton for submission to a public health laboratory. Physicians should contact their local health department for the availability of tick identification and isolation of *B burgdorferi*.

The case reported in San Bernardino has not been proved to be Lyme disease; however, the fact that the serologic test was negative may have been due to early antibiotic treatment. In one study, among ten patients with early Lyme disease (erythema migrans only) who were treated early in their course, only one had an antibody response.[2] The importance of this case is that it led to the identification of ticks positive for *B burgdorferi* in an area previously thought to be free of the organism. It also illustrates the difficulty in confirming the diagnosis of Lyme disease when early treatment is instituted. Readers are referred to several recent reviews of the diagnosis and treatment of Lyme disease.[3-5]

Although the risk appears to be low, physicians should be aware that Lyme disease may be contracted in San Bernardino and Orange counties and perhaps other locations in southern California. Public health authorities should continue surveillance for infected tick vectors and human cases of Lyme disease. The appearance of the causative agent of Lyme disease in southern California indicates that reported cases may not remain confined exclusively to previously endemic areas of the country.

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Commentary

Personal Renewal

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EDITOR'S NOTE: *After John Gardner's presentation on "Self-Renewal" to* THE WESTERN JOURNAL OF MEDICINE *Editors' Meeting,* Joseph Murphy, MD, Special Editor for Wyoming, asked the former Secretary of Health, Education, and Welfare, "Where are you in your life's cycle?" Dr Gardner, who is 80 years old, answered, "When Chief Justice Oliver Wendell Holmes, Jr, was in his 90s, he was asked a similar question and said, 'I'm like a race horse cantering along after the race is over, cooling down.' Well, I'm nowhere near cantering! I'm still in the race, pushing the world."*

John Gardner, who received his undergraduate degree from Stanford and PhD from the University of California, Berkeley, taught at the college level for several years before he joined the Carnegie Foundation. As president of Carnegie Corporation and Carnegie Foundation for the Advancement of Teaching, he began to "push the world" toward education and in 1964 received the country's highest civilian honor, the Presidential Medal of Freedom. He has also pushed it toward political reform by founding Common Cause, toward grass-roots political action by founding the Urban Coalition, toward leadership training by founding the White House Fellows program, and toward volunteerism by founding the Independent Sector (a coalition of for-profit and not-for-profit organizations and foundations). His books, including Excellence, Self-Renewal, No Easy Victories, *and* On Leadership, *have pushed readers to new understanding of themselves and of organizations and to higher levels of creativity and energy to get important work done. His current research focuses on discovering and defining the characteristics of healthy, vital communities. His call to "keep on keeping on," indeed, to push the world, leads to constructive change. Active people become effective people, infused with the energy and optimism that good hard work inspires. I think you will find this paper as invigorating to read as it was to hear.*

LINDA HAWES CLEVER, MD

*San Francisco, Calif, April 4, 1992.

I once wrote a book called *Self-Renewal* that deals with the decay and renewal of societies, organizations, and individuals. I explored the question of why civilizations die and how they sometimes renew themselves and the puzzle of why some men and women go to seed while others remain vital all of their lives. It's the latter question that I shall deal with at this time. I know that you personally are not going to seed. But the person next to you may be in fairly serious danger.

Not long ago, I read a splendid article on barnacles. I do not want to give the wrong impression of the focus of my reading interests. Sometimes days go by without my reading about barnacles, much less remembering what I read. But this article had an unforgettable opening paragraph. "The barnacle," the author explained, "is confronted with an existential decision about where it's going to live. Once it decides . . . it spends the rest of its life with its head cemented to a rock. . . ." For a good many of us, it comes to that.

Some men and women seem to run out of steam in midcareer. You have known such people—feeling secretly defeated, maybe somewhat sour and cynical, or perhaps just vaguely dispirited.

We have to face the fact that most men and women out there in the world of work are more stale than they know, more bored than they would care to admit. Boredom is the secret ailment of modern life. A successful executive said to me the other day, "How can I be so bored when I'm so busy?" And I said, "Let me count the ways." Logan Pearsall Smith said that boredom can rise to the level of a mystical experience, and if that's true I know some very busy adults who are among the great mystics of all time.

I have watched a lot of midcareer people, and Yogi Berra says you can observe a lot just by watching. I have concluded that most people enjoy learning and growing. And many are clearly troubled by the self-assessments of midcareer.

Such self-assessments are no great problem when you are young and moving up. The drama of your own rise is enough. But when you reach middle age, when your energies are not what they used to be, then you will begin to wonder what it all added up to, you will begin to look for the figure in the carpet of your life. I have some simple advice for you when you begin that process. Don't be too hard on yourself. Look ahead. Someone said that "Life is the art of drawing without an eraser." And above all, do not imagine that the story is over. Life has a lot of chapters.

I said in *Self-Renewal* that we build our own prisons and serve as our own jailkeepers. I no longer completely agree with that. I still think we are our own jailkeepers, but I have concluded that our parents and the society at large have a hand in building our prisons. They create roles for us—and self-images—that hold us captive for a long time. The person intent on self-renewal will have to deal with ghosts of the past—the memory of earlier failures, the remnants of childhood dramas and rebellions, and the accumulated grievances and resentments that have long outlived their cause. Sometimes people cling to the ghosts with something almost approaching pleasure—but the hampering effect on growth is inescapable.

The more I see of human lives, the more I believe the business of growing up is much longer drawn out than we pretend. If we achieve it in our 30s, even our 40s, we are doing well. To those of you who are parents of teenagers, I

(Gardner JW: Personal renewal. West J Med 1992 Oct; 157:457-459)

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can only say, "Sorry about that." For this generation of kids, the rule is, "Out of the house by 40."

There's a myth that learning is for young people. But as the proverb says, "It's what you learn after you know it all that counts." The middle years are great, great learning years. Even the years past the middle years. I took on a new job after my 77th birthday—and I'm still learning.

It's a good idea to pause occasionally for an *inward* look. By midlife most of us are accomplished fugitives from ourselves. Sooner or later you have to come to terms with yourself. You have to grasp what S. N. Behrman meant when he said, "At the end of every road you meet yourself." You may not get rid of all of your hang-ups, but you learn to control them to the point that you can function productively and not hurt others.

You have to come to understand your impact on others. It's interesting that even in the first year of life you learn the impact that a variety of others have on you, but as late as middle age many people have a very imperfect understanding of the impact they have on others. The hostile person keeps asking, "Why are people so hard to get along with?"—never reflecting on the fact that he's creating his own environment. In some measure we all create our own environments. You may not yet grasp the power of that truth to change your life.

Of course, failures are a part of the story, too. Everyone fails. Joe Louis said, "Everyone has to figure to get beat some time." The question is not did you fail but did you pick yourself up and move ahead? And there is one other little question: "Did you collaborate in your own defeat?" A lot of people do. Learn not to.

But there is something I know about you that you may or may not know about yourself. You have within you more resources of energy than have ever been tapped, more talent than has ever been exploited, more strength than has ever been tested, more to give than you have ever given.

You know about some of the gifts that you have left undeveloped. Would you believe that you have gifts and possibilities you don't even know about? It's true.

It isn't possible to talk about renewal without touching on the subject of motivation. Someone defined horse sense as the good judgment horses have that prevents them from betting on people. But we have to bet on people—and I place my bets more often on high motivation than on any other quality except judgment. There is no perfection of techniques that will substitute for the lift of spirit and heightened performance that comes from strong motivation. The world is moved by highly motivated people, by enthusiasts, by men and women who want something very much or believe very much.

The nature of one's personal commitments is a powerful element in renewal, so let me say a word on that subject.

I once lived in a house where I could look out a window as I worked at my desk and observe a small herd of cattle browsing in a neighboring field. And I was struck by a thought that must have occurred to the earliest herdsmen tens of thousands of years ago. You never get the impression that a cow is about to have a nervous breakdown. Or is puzzling about the meaning of life.

Humans have never mastered that kind of complacency. We are worriers and puzzlers, and we want meaning in our lives. I am not speaking idealistically; I am stating a plainly observable fact about men and women. It's a rare person who can go through life like a homeless alley cat, living from day to day, taking its pleasures where it can, and dying unnoticed.

That is not to say that we have not all known a few alley cats. But it is not the norm. It just is not the way we are built.

For many this life is a vale of tears; for no one is it free of pain. But we are so designed that we can cope with it if we can live in some context of meaning. Given that powerful help, we can draw on the deep springs of the human spirit, to see our suffering in the framework of all human suffering, to accept the gifts of life with thanks and endure life's indignities with dignity.

We tend to think of youth and the active middle years as the years of commitment. As you get a little older, you are told you have earned the right to think about yourself. But that is a deadly prescription! People of every age need commitments beyond the self, need the meaning that commitments provide. Self-preoccupation is a prison, as every self-absorbed person finally knows. Commitments to larger purposes can get you out of prison.

Another significant ingredient in motivation is one's attitude toward the future. Optimism is unfashionable today, particularly among intellectuals. Everyone makes fun of it. Someone said, "Pessimists got that way by financing optimists." But I am not pessimistic and I advise you not to be. As the fellow said, "I'd be a pessimist but it would never work."

I can tell you that for renewal, a tough-minded optimism is best. The future is not shaped by people who do not believe in the future. Men and women of vitality have always been prepared to bet their futures, even their lives, on ventures of unknown outcome. If they had all looked before they leaped, we would still be crouched in caves sketching animal pictures on the wall.

But I did say tough-minded optimism. High hopes that are dashed by the first failure are precisely what we do not need. We have to believe in ourselves, but we must not suppose that the path will be easy. It's tough. Life is painful, and rain falls on the just, and Mr Churchill was not being a pessimist when he said, "I have nothing to offer but blood, toil, tears, and sweat." He had a great deal more to offer, but as a good leader he was saying it was not going to be easy. He was also saying something that all great leaders say constantly—that failure is simply a reason to strengthen resolve.

We cannot dream of a utopia in which all arrangements are ideal and everyone is flawless. Life is tumultuous—an endless losing and regaining of balance, a continuous struggle, never an assured victory.

Nothing is ever finally safe. Every important battle is fought and re-fought. We need to develop a resilient, indomitable morale that enables us to face those realities and still strive with every ounce of energy to prevail. You may wonder if such a struggle—endless and of uncertain outcome—is more than humans can bear. But all of history suggests that the human spirit is well fitted to cope with just that kind of world.

Remember I mentioned earlier the myth that learning is for young people. I want to give you some examples to counter the myth. In a piece I wrote for *The Reader's Digest* not long ago, I gave what seemed to me a particularly interesting true example of renewal. The man in question was 53 years old. Most of his adult life had been a losing struggle against debt and misfortune. In military service he received a battlefield injury that denied him the use of his left arm. He was also seized and held in captivity for five years. Later he held two government jobs, succeeding at neither. At 53 he

was in prison—and not for the first time. Would you bet on this man? You can see all the personnel directors you have ever known shaking their heads gloomily. But there in prison, he decided to write a book, driven by heaven knows what motive—boredom, the hope of gain, emotional release, creative impulse—who can say? And the book turned out to be one of the greatest ever written, a book that has enthralled the world for over 350 years. The prisoner was Cervantes; the book, *Don Quixote*.

Another example is Pope John XXIII, a serious man who found a lot to laugh about. The son of peasant farmers, he once said, "In Italy there are three roads to poverty—drinking, gambling, and farming. My family chose the slowest of the three." When someone asked him how many people worked in the Vatican, he said, "Oh, about half." He was 76 years old when he was elected Pope. Through a lifetime in the bureaucracy, the spark of spirit and imagination had remained undimmed, and when he reached the top he launched the most vigorous renewal that the Catholic Church has known in this century.

Still another example is Winston Churchill. At age 25, as a correspondent in the Boer War, he became a prisoner of war, and his dramatic escape made him a national hero. Elected to Parliament at 26, he performed brilliantly, held high cabinet posts with distinction, and at 37 became First Lord of the Admiralty. Then he was discredited, unjustly, I believe, by the Dardanelles expedition—the defeat at Gallipoli—and lost his admiralty post. There followed 24 years of ups and downs. All too often the verdict on him was, "Brilliant but erratic . . . not steady, not dependable." He had only himself to blame. A friend described him as a man who jaywalked through life. He was 66 before his moment of flowering came. Someone said, "It's all right to be a late bloomer if you don't miss the flower show." Churchill did not miss it.

From those examples I have given, I hope it is clear that the door of opportunity does not really close as long as a person is reasonably healthy. The question is what lies ahead. A person may not go to jail and write a novel, or become Pope. But as long as the spirit is undimmed, new and rich patterns of meaning in life can be created as you grow older.

Many years ago in a speech to high school graduates, I concluded with a paragraph on the meaning in life. The speech was reprinted over the years, and 15 years later that final paragraph came back to me in a rather dramatic way, really a heartbreaking way.

A man wrote to me from Colorado saying that his 20-year-old daughter had been killed in an auto accident some weeks before and that she was carrying in her billfold a paragraph from a speech of mine. He said he was grateful because the paragraph—and the fact that she kept it close to her—told him something he might not otherwise have known about her values and concerns. I cannot imagine where or how she came across the paragraph, but here it is.

Meaning is not something you stumble across, like the answer to a riddle or the prize in a treasure hunt. Meaning is something you build into your life. You build it out of your own past, out of your affections and loyalties, out of the experience of humankind as it is passed on to you, out of your own talent and understanding, out of the things you believe in, out of the things and people you love, out of the values for which you are willing to sacrifice something. The ingredients are there. You are the only one who can put them together into that unique pattern that will be your life. Let it be a life that has dignity and meaning for you. If it does, then the particular balance of success or failure is of less account.

Editorials

'New Habits of Mind'—Bridging the Gap Between Public Health and Clinical Medicine

As recently as 200 years ago medicine and surgery existed as separate spheres, without common training, collaborative practice, or substantive communication. An analogous chasm divides public health and clinical medicine to this day, despite decades of change in medical practice. Major efforts to promote research and education in the fields of preventive cardiology and pulmonary medicine have succeeded in modifying physicians' approaches to the identification and management of a variety of risk factors, have reduced risk-taking behaviors among much (though by no means all) of the general population, and have been accompanied by sharp declines in mortality from cardiovascular causes. Family practice and general internal medicine have incorporated clinical epidemiology and behavioral medicine into residency training and medical practice, so that questions about immunization status, sexual practices, substance abuse, and symptoms of depression now constitute good medical practice. Yet rates of measles, sexually transmitted diseases, murder, and adolescent suicide have risen, along with homelessness, lack of access to health care, underemployment, and unemployment. Public health officials, admittedly hampered by minuscule funding, have been no more successful and have limitations of their own. From Ellis Island to Tuskegee, Alabama, to Oregon, they have periodically detached themselves entirely from individual human beings, with appalling results. Physicians in clinical practice regard regulatory intervention and population study as alien activities. The admonitions of occupational medicine are often just one more voice faintly buzzing in the background.

In this issue of the journal, Rosenstock and colleagues make themselves heard clearly.[1] They report the experience of the first ten years of an academic occupational medicine clinic firmly rooted in a department of medicine and in clinical practice. The clinic's three goals include diagnosing the work-relatedness of disease in individual patients, screening groups of workers for adverse health effects, and training physicians and other professionals (both generalists and specialists) in the field. It makes occupational and environmental medicine visible and accessible within traditional referral patterns: physicians in practice can pick up the phone and reach a colleague.

Through the sheer force of will, these clinics have defined occupational medicine as an academic medicine specialty like cardiology or nephrology, only more so. Academicians wishing to recapture Osler's "art of observation . . . [founded on] attention to subtle detail and unbiased assessment" can use occupational medicine: Listen to Sir Arthur Conan Doyle's description of the diagnostic skills of a contemporary Edinburgh surgeon:

> "Gentlemen," he would say to us students standing around, "I am not quite sure whether this man is a cork-cutter or a slater. I observe a slight callus, or hardening, on one side of his fourth finger and a little thickening on the outside of his thumb, and that is a sure sign that he is either one or the other."[2(p864)]

Medical educators who find pure observational virtuosity too cold emphasize the need to maintain empathy and contact with a patient through history taking.[3] Here, too, the occupational history can play a role in recognizing the patient as an adult and validating his or her abilities. Furthermore, the occupational history is a way of gaining insight into cultural, racial, and class diversity in an arena where some of the boundaries are shared. It fosters listening skills.

It is not enough, however, to argue that occupational medicine adds to the clinical acumen and empathy of medical practitioners. The goal must be to merge clinical and public health traditions while recognizing individual areas of expertise. The easy access and flow of information provided by the academic occupational medicine clinics is a vitally important step. Equally important is establishing the prevalence of disease in at-risk populations, a function performed to some extent by the screening activities of the clinics. But clinics screen groups already known to be at risk from well-established hazards such as asbestos and do not provide population surveys on a scale necessary to address the issue of prevalence. Physicians in primary care practice see many patients with diarrhea, or irritability and depression, or Parkinson's disease, and evaluating all of them for organophosphate or lead or manganese poisoning is inappropriate. But what about subgroups at particular risk? Physicians need to know whether their patients are farm workers, construction workers, or welders and whether they have reentered sprayed fields or have done bridge-repair work recently. They can ask the patient and catch a glimpse of the patient's life that will be useful in establishing a therapeutic alliance.

The sad truth is that once the exposure history has been obtained, the prevalence data that would make it meaningful do not exist. It is as if we were asked to evaluate a patient with chest pain without knowing the effects of age and sex. Physicians referred fully a quarter of the patients who were seen in this clinic for diagnostic purposes, but physician-referred patients were less likely than the clinic population as a whole to have occupationally related disease. In fact, patients referred by unions (10% of the total) were five times as likely to have occupational illness as patients referred by physicians. Demographics clearly play a part in this; unions generally refer from a population known to have an exposure, whereas physicians may be referring their diagnostic puzzles. I suspect that physician discomfort with the regulatory process may also be a factor not shared by referring unions. In both explanations, unions appear to be more comfortable than physicians with the public health aspects of occupational medicine. As a profession and as a society, we need to define the physician's role more broadly and set reasonable goals for practice.

The Occupational Medical Practice Committee of the American College of Occupational and Environmental Medicine has attempted to do this. Their "scope of practice" guidelines include participation in developing governmental health and safety regulations as an essential component of practice, along with the diagnosis and treatment of occupational illness and the evaluation, inspection, and abatement of workplace hazards.[4] While these define occupational and environmental medicine as a specialty, the framework they teach for viewing the role of physicians is useful. Regulation and abatement (enforcement) are legitimate areas of medical practice.

The absence of adequate information about disease prevalence does not entirely exonerate practicing physicians. Their referral patterns should reflect some basic level of competency achieved during medical school or primary care residency training. Treating physicians evaluate exposure history and health outcome in patients and attempt to determine whether a biologically plausible connection can be made. This is a straightforward medical function, requiring physicians to use reference sources of information (including occupational medicine clinics) and to interpret uncertainty to their patients. The implications for false-positive as well as false-negative findings are substantial, particularly where nonoccupational environmental exposures are concerned. Anxiety about low levels of exposure may cause greater damage than the exposure itself, and some of these difficulties can be avoided by using basic pharmacologic principles regarding routes of absorption and dose-response relationships as well as positive criteria for alternative diagnoses. If a public health approach were added, students and practitioners would use new conceptual frameworks and an enlarged scope of resources rather than attempt to ingest yet one more set of facts.

By introducing some of their basic tools, public health practitioners might offer clinicians an antidote for that classic source of workplace stress, responsibility without control. Borrowing again from work design models, increasing the diversity of tasks the worker (physician) is competent to handle might also enhance job satisfaction and prevent repetitive strain injuries (burnout?).

Public health professionals benefit from clinical perspectives as well. Lung cancer in a 32-year-old is a sentinel event of a different order of magnitude than when it occurs in a 72-year-old; regarding the "bullet as pathogen" may provide new insight into the root causes of violence in our society.[5] Occupational and environmental illness is one of many areas in which medicine and public health offer each other fresh approaches to education and practice.

Maulitz describes the coming together of medicine and surgery in the wake of the French Revolution in terms that compel:

> But what happens when two [traditions], once in proximity but with disparate conceptions of health and disease, suddenly find themselves forced to make common cause? Precipitously, institutions and professional groups must grasp for means of accommodation. Intellectual resources must be discovered or created to help adjust to shifts in worldly resources. Covering explanations must be found. New habits of mind must be developed to permit the rupture and rethinking of old, exclusive roles and relationships. All of these things are accomplished through education and communication, through the assimilation and dispersion of symbols and ideas.[6(p228)]

In the aftermath of the Cold War, perhaps we can do the same with clinical medicine and public health.

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Complications of Asplenia and Hyposplenism—Persistent Uncertainties

After once being considered almost as unnecessary as the appendix, the spleen has been increasingly recognized in recent years as an important component of host defense against infection. This new-found respect is due in large part to the increasing appreciation of the syndrome of overwhelming postsplenectomy infection, especially its most characteristic presentation as fulminant septicemia—most often with an encapsulated organism such as *Streptococcus pneumoniae* and often without a discernible focus—with disseminated intravascular coagulation and multisystem dysfunction. In this issue Brigden provides a case history and literature review that illustrate many of the typical features of overwhelming postsplenectomy infection, including its sudden onset and rapid progression in an apparently healthy person and frequent progression to death despite intensive treatment.[1] The inexorable downhill course of the patient described, despite vigorous treatment apparently within a few hours of initial symptoms, also highlights some of the many unresolved questions in predicting and preventing this devastating event.

The uncontrollable nature of pneumococcal infection in this patient presumably reflects the loss of the contribution of the spleen to host-defense functions such as the filtration of particles from the blood stream and antibody and other opsonin production. Because these functions may be preserved to varying degrees in different situations, expectations and precautions for an individual patient depend on the highly imperfect information currently available to answer several questions. First, how common is overwhelming postsplenectomy infection? Second, who is at risk besides those with known removal of all splenic tissue, and can levels of risk be determined? Third, what measures are worthwhile for preventing overwhelming postsplenectomy infection, including the early treatment of suspected sepsis to avoid its progression to "overwhelming"?

The absolute risk of fulminant infection in asplenic patients has been difficult to establish because of the lack of large cohort studies with consistent follow-up. A recent survey of events in an Australian population provides one of the larger groups thus far available, studied over a period designed to minimize the modifying effects of immunization and antimicrobial prophylaxis.[2] This series yielded six late deaths from infection—although not all of these were categorized as overwhelming postsplenectomy infection—over 7,825 person-years of observation. Allowing for the exclusion of the immediate perioperative period, the resulting figure of 1 septic death per 1,305 person-years is within the range of a selection of earlier studies,[3] but this selection tends to show wide variability, a higher incidence in infants and children, and variability according to the reason for splenectomy.

Situations short of documented splenectomy offer still fewer prospects for predicting risk. Congenital asplenia may

be predictably associated with specific congenital anomalies and with susceptibility to sepsis[4] but may go unrecognized in patients without obvious indicators. The association of functional hyposplenism and severe infections, especially pneumococcal sepsis, is best documented in sickle cell anemia.[5] Overwhelming pneumococcal sepsis and splenic abnormalities have been reported anecdotally in immunologic disorders such as systemic lupus erythematosus.[6] Other diseases such as celiac disease and ulcerative colitis may be associated with splenic dysfunction,[7] but there is little information on the specific incidence of infection. There have been occasional case reports of overwhelming pneumococcemia in these disorders[8] but also in persons without a known predisposition,[9] and relative risks are unclear.

The usefulness of laboratory assays of splenic dysfunction in predicting risks of infection is debatable. Occasionally the detection of Howell-Jolly bodies on a routine blood smear may be a clue to congenital asplenia,[10] but finding these nuclear remnants in erythrocytes of patients with other disorders such as celiac disease has not generally been documented as directly predicting the degree of risk of infection.[11] The presence of ectopic splenic tissue, negatively correlated with Howell-Jolly body counts, was not significantly related to immunoglobulin levels in one study.[12] Furthermore, Howell-Jolly bodies appear to reflect only the function of the splenic red pulp rather than the combination of filtering activity and mediator production involved in the complex host-defense role of the spleen.[13] Thus, if the laboratory notes Howell-Jolly bodies on a blood smear and alerts the primary physician to this finding, this may facilitate screening for the presence and function of the spleen where abnormalities were not previously suspected but will not necessarily alter management if a condition associated with hyposplenism has already been documented.

Given the persistent uncertainty in defining risk groups, in most instances specific tests of splenic function may contribute little to deciding a patient's risk. Even if such a relationship could be established, the ability of splenic function to wax and wane in the same patient over time[6,7] would prevent the confident prediction of future risks in many hyposplenic patients. Because hyposplenism has also been reported as a consequence rather than a cause of infection,[14] documented hyposplenism at the time of sepsis is not even necessarily accurate in retrospectively assigning a patient to a high-risk group.

Although the criteria and prognostic significance of subtle degrees of splenic dysfunction remain poorly defined, there is clear enough documentation of the risk of sepsis in surgical or congenital asplenia and a few other disorders such as sickle cell anemia to warrant serious attention to preventive measures. Methods to avoid surgical asplenia by doing salvage procedures are increasingly widely accepted,[15] and autotransplantation may be used when repair is not possible, although postsplenectomy sepsis has been reported even in the presence of transplanted regenerated tissue.[16] Because partial efficacy of these compromise measures has been reported but is not well quantitated, patients who have undergone salvage procedures should still be considered candidates for other preventive measures such as immunization.

Recommendations on immunizations for asplenic or hyposplenic patients have undergone some recent changes. Most such recommendations have focused on pneumococcal vaccine because *S pneumoniae* is the most important (although by no means the only) cause of overwhelming postsplenectomy infection and have been based on the assumption that immunization is likely to offer more benefits than risks, even though these patients may also have suboptimal responses to immunizing agents. Recently revised recommendations from the Centers for Disease Control now suggest that meningococcal as well as pneumococcal vaccine be given to adults "with splenic dysfunction or anatomic asplenia,"[17(p14)] that *Haemophilus influenzae* vaccine may also be considered, and that pneumococcal revaccination be "strongly considered" after six years for asplenic patients. If plans for elective splenectomy permit giving meningococcal and pneumococcal vaccines at least two weeks before the operation, the recommendations suggest this interval. The American Academy of Pediatrics recommends pneumococcal and meningococcal vaccine for asplenic children 2 years of age or older, in addition to the usual schedule of *H influenzae* immunization.[18]

Because of the incomplete protection offered by these vaccines, there has been substantial interest in antimicrobial chemoprophylaxis, usually with penicillin to try to avert serious pneumococcal infections. This is generally recommended for young children who are asplenic,[18] but there is substantial disagreement on its utility for older persons. Long-term oral penicillin use has been shown to protect against serious pneumococcal disease in young children with sickle cell anemia,[5] who have an extremely high risk of these infections, but the data in other populations are inadequate. This strategy obviously does not protect against other organisms causing postsplenectomy sepsis that may not be susceptible to penicillin, and even fulminant pneumococcal infections have been reported in patients allegedly receiving prophylaxis.[1,19] Especially because as many as a third of surveillance urine specimens may show no penicillin present during long-term prophylaxis even in highly motivated and well-informed populations,[19] pneumococcal sepsis should be considered as a possibility in asplenic patients with febrile illness regardless of what prophylactic measures have been used.

Perhaps the most critical but least-studied decision in the prevention of overwhelming postsplenectomy infection takes place (or should) at the first sign of febrile illness. Certainly patients should be aware of the importance of seeking medical care for even minor febrile illnesses and of informing all care givers of their asplenia. Physicians need to be aware of the rapidity with which sepsis in asplenic patients can progress after nonspecific initial symptoms and of the need to at least entertain similar diagnoses in patients in whom splenic hypofunction is suspected. While there is not substantial comparative information on the outcome of early antibiotic therapy versus watchful waiting, the potential for irreversible multisystem deterioration within a matter of hours would seem to argue in favor of instituting antibiotic therapy—active at least against the pneumococcus, and often against other encapsulated organisms—as soon as possible when a diagnosis of postsplenectomy sepsis is entertained. A recent Scandinavian study credits a policy of recommending immediate penicillin therapy for all febrile illnesses (even before the patient is seen by a physician), together with immunization, as having greatly decreased the incidence of serious pneumococcal infection in asplenic children.[20] Although the control group was historic rather than concurrent, the results deserve attention partly because they would be compatible with a

theoretic advantage of instituting treatment at the time the organism first invades the blood stream and before high-grade bacteremia can develop.

Overwhelming postsplenectomy infection is fortunately a rare event, but its very rarity has contributed to the many gaps in understanding how to prevent infection in the first place and how to prevent progression to multiorgan system failure when infection occurs. Immunization is among the least controversial issues, along with patient education—insofar as the facts to transmit are known—and early assessment of febrile illnesses, partly because these are interventions with little intrinsic morbidity and clear analogies to a broad range of other medical situations. The risks and benefits of antibiotic prophylaxis beyond early childhood, and the delineation of basic criteria for the early institution of therapeutic antibiotics, are more difficult to determine because there are more adverse aspects of overtreatment—including toxicity, the selection of resistant organisms, and sometimes the disruption of the quality of life—to be weighed against an unknown success rate in defusing an explosive infection that is uncommon in itself but devastating when it occurs. It has been suggested that multicenter trials are needed to define the optimal use of splenic autotransplantation,[21] and it could be argued that a similar approach is needed to define the optimal use of antibiotics to prevent cases like the one Brigden describes. Until and unless trials on such a heroic scale become available, these latter decisions must depend largely on evaluation tailored to each patient's unique situation.

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Treatment Strategies in the Prevention of Tuberculosis

THE RESURGENCE OF tuberculosis, which began to be reported in 1986, has created new concerns about how to control this persistent and ever-changing disease. Though considered "down, but not out," to paraphrase John Murray, MD, at the annual Amberson Lecture of the American Thoracic Society,[1] tuberculosis is clearly returning with a vengeance.[2,3] Reasons for its resurgence are the growing number of patients with immunosuppression due to human immunodeficiency virus (HIV) infection[4,5] and our aging population[6] with the immunodeficiency of age, malnutrition, and the use of drugs that may promote tuberculosis reactivation.[5]

These major factors plus the presence of immigrants previously infected with *Mycobacterium tuberculosis*, but without clinically detectable disease and often harboring drug-resistant organisms, create new challenges in our quest to control and eradicate tuberculosis from this country by the year 2010.[7] This goal will never be achieved using current tuberculosis prevention strategies.

Today national policy dictates that isoniazid chemoprophylaxis be given all persons at high risk of contracting active tuberculosis. These are primarily patients with known contacts with infected persons, patients with a well-documented skin test conversion, and patients with chest x-ray film abnormalities as a minimum. Because most of these "high-risk persons" actually have non-culture-proven but active disease, they should be treated, but would it not make more sense to treat with two drugs for greater effectiveness? So-called preventive therapy with isoniazid alone is widely held to be 90% effective. Does this mean a 10% failure rate? The downside of adding a companion drug such as ethambutol would, of course, be increased cost and some slight increase in toxicity. At this time we have no controlled clinical trials to determine whether isoniazid alone is as effective as the use of two drugs in these patients.

Today we face a new tuberculosis epidemic in this country and throughout the world. Accordingly we must develop new strategies to prevent and treat this disease, particularly in high-risk groups, lest the epidemic become uncontrolled. One of the most advocated approaches to tuberculosis prevention and control is the "preventive therapy" of an expanded spectrum of risk groups, including patients infected with HIV or who have the acquired immunodeficiency syndrome (AIDS). Shelley Salpeter, MD, elsewhere in this issue offers specific advice about preventive therapy strategies for the 1990s, including advice about therapy for HIV-infected persons.[8] This advice, based on contemporary knowledge of tuberculosis epidemiology and drug susceptibility patterns in this country, represents an extrapolation from inadequate data. None of it is based on solid evidence from controlled clinical trials, particularly in HIV-infected persons. It is known that HIV-infected persons, even those with clinical AIDS, respond well to the major antituberculosis chemotherapy agents given in various combinations, but more anemia

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
BCG = bacille Calmette-Guérin [vaccine]
HIV = human immunodeficiency virus

occurred with tuberculosis chemotherapy and zidovudine than when zidovudine was given alone.[9]

There is also some controversy over what criteria should be used to designate an infected person.[10] Lowering the "threshold" for the previously accepted "standard" of 10 mm of induration for intermediate-strength purified-protein derivative—that is, 5 tuberculin units—has been suggested, and increasing the threshold level of a substantial tuberculin reaction in those considered to be at lowest risk has also been advised.[11] Thus it is suggested that a 5-mm reaction in HIV-infected persons should be considered significant; those at lowest risk should have 15 mm of induration before preventive therapy is considered. Possibly even 2 mm of induration might be taken as evidence of infection, according to current advice. But I doubt that many experts could readily distinguish a 2-mm reaction from the pinprick itself. Perhaps all HIV-positive persons should be given isoniazid chemoprophylaxis as "preventive therapy," regardless of the degree of tuberculin reactivity, as has also been suggested.[12]

Again, the trouble with this advice is that it is not based on adequate prospective controlled clinical trials. Because we do not know whether isoniazid chemoprophylaxis is good, bad, or indifferent in patients infected with HIV or who have AIDS, why not do controlled clinical trials to answer these key questions? Such trials were recently successfully accomplished in Hong Kong in patients with silicosis, known to be among those at highest risk for the development of active and virulent clinical tuberculosis.[13] In this trial, isoniazid therapy was compared with the use of rifampin and placebo and with both isoniazid and rifampin versus placebo. In this study both isoniazid and rifampin proved to be highly effective in preventing the emergence of clinical tuberculosis compared with placebo. The combination was no more effective than either single drug in this setting. It was interesting that thus far, no isoniazid or rifampin resistance developed, but the later emergence of drug resistance remains a possibility.

Why not do similar studies in well-defined groups of HIV infection? Answers about the efficacy and safety of isoniazid or other forms of preventive therapy could be known in a relatively short time, considering the poor prognosis of HIV-infected patients in general and AIDS patients in particular.

How could isoniazid preventive therapy cause harm? The fact of fatal isoniazid hepatitis has been known for about 30 years but scarcely reported. More recently Moulding and coworkers found 20 cases of fatal isoniazid hepatitis in one state where the drug was used for prevention in 19 of 20 of these patients,[14] and the Centers for Disease Control recently reported 177 cases.[15] Add to this the risk of isoniazid peripheral neuritis, toxic reactions from drug overdose where isoniazid is a frequently used suicide agent, particularly in Native Americans,[16,17] miscellaneous less serious reactions such as isoniazid-related arthritis, and drug interactions, and it becomes clear that this is not a perfectly safe drug. The possible emergence of isoniazid-resistant organisms, where the drug is used alone, though rare, must also be considered and further studied.

Another problem with so-called preventive therapy is conceptual. We use the tuberculin reaction as evidence for infection, but the tuberculin reaction can be negative in the face of florid tuberculosis such as in older patients, in patients with disseminated disease, and in HIV-infected persons with tuberculosis. Conversely, the tuberculin skin test may be strongly positive, that is, more than 15 mm of induration, in many patients with less than a 5% chance of ever having clinical disease. Thus the tuberculin skin test is of only modest value in case finding. In addition, infected persons may have more actively multiplying organisms than is clinically evident, particularly in extrapulmonary forms of disease. Is it prudent to treat with only one drug? Would not a two- or even three-drug combination be more likely to be effective, particularly in cases where the chance of isoniazid resistance is present, such as in immigrants?

For any kind of preventive intervention to be recommended for any population requires the establishment of the intervention's validity.[18] The randomized controlled clinical trial is the most conclusive, and expert opinion the least powerful, indicator of validity.[18]

For all of the above considerations, until guided by controlled clinical trials, the use of "chemoprophylaxis" or preventive therapy must be guided by clinical judgment. Decision analysis focusing on risk:benefit ratios can also be useful.[19,20] The use of decision analysis to guide isoniazid chemoprophylaxis is not new and was first seriously suggested more than a decade ago.[21] An accompanying editorial by a major contributor to the knowledge about tuberculosis epidemiology and prospects for its prevention asked for more data at that time.[22] Alas, the design and conduct of studies to help guide the choice of isoniazid in various populations did not occur, and we are thus left with therapeutic choices based on model rather than hard data. Now, with HIV infection, controlled clinical trials are desperately needed to guide the choice of preventive therapeutic strategies.

A more recent use of decision analysis suggests that ethnicity, age, and sex must be factored into the choice of isoniazid chemoprophylaxis in persons who are not HIV-positive.[20] In general, the benefit of isoniazid chemoprophylaxis appears to favor all groups except black women older than 50. But many would remain cautious about using this drug for so-called prevention for those older than 35.

The guidelines and advice concerning tuberculosis chemoprophylaxis offered by Salpeter, if carefully followed, will probably do more good than harm—at least until there is better guidance through controlled clinical trials.

Finally, are there alternatives to be considered in the prevention of tuberculosis? Although the official position of the American Thoracic Society and the Centers for Disease Control is against the use of the bacille Calmette-Guérin vaccine (BCG) in this country, certain experts in our country and elsewhere in the world disagree with this dictum.[22-24] Of course, HIV-positive patients should not be given BCG because their impaired immune state might foster the development of clinical BCG infection. But why not use BCG in young, otherwise healthy persons who are tuberculin-negative, such as HIV-negative health care workers? The vaccine has been used worldwide as a control measure since 1921, with the greatest demonstrable success in children.[25] Unfortunately, various BCG strains have been used in different countries with different results. Also, there is no identifiable immunologic counterpart of protective immunity.[24] The argument that vaccination will negate the value of the tuber-

culin skin test as a case-finding tool is countered by evidence that the age at vaccination has an important bearing on tuberculin skin testing 10 to 25 years later.[26] Infants vaccinated with BCG in Canada had no greater tuberculin reaction than nonvaccinated infants in a follow-up study.[26] Should not infants in HIV-infected high-risk areas such as New York City be vaccinated?

Nearly everywhere I have traveled outside the United States, I am asked why we do not use BCG in certain high-risk groups as is commonly done elsewhere in the world including Canada. All I can answer, with a shrug, is, "There is no reason. It's just national policy."

My views on the prevention of tuberculosis may stir controversy. That is intended because it is high time we reconsider the dogma and policies of the past decades that have failed to control tuberculosis in this country.

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Nonsteroidal Anti-inflammatory Drugs and Ulcers

ALTHOUGH ASPIRIN has been used for medicinal purposes for more than a century, only in the past five years have the gastrointestinal complications of this agent and the other nonsteroidal anti-inflammatory drugs (NSAIDs) become widely recognized as serious problems. As reviewed by Richard Babb, MD, elsewhere in this issue, NSAIDs have deleterious effects on the entire gastrointestinal tract from the esophagus to the colon, although the most obvious clinical effect is on the gastroduodenal mucosa.[1] My comments focus on a few points regarding the etiology of NSAID-induced injury and the clinical consequences of this injury. Nonsteroidal anti-inflammatory drugs may cause or may precipitate peptic ulcers, but little is known about the actual pathophysiologic mechanisms involved. A number of controversial points pertain to the delivery to the mucosa, the mode of action, and the nature of the injury caused by NSAIDs.

NSAID Delivery to the Gastroduodenal Mucosa

These drugs are delivered to the gastric and duodenal mucosa by three routes:

- Aspirin and the other NSAIDs that are soluble at both acidic pH and weak acids can be dramatically and rapidly concentrated in the gastric mucosa by pH-dependent trapping. Weak acids are un-ionized at an acidic pH of gastric secretions and can freely cross the gastric cell membranes. When these weak acids encounter the neutral pH of the cell interior, however, they give up a hydrogen ion and, once negatively charged, are unable to exit the cell. Concentrated in mucosal cells, their potential damaging effects are amplified, contributing to the damage occurring within minutes after intragastric administration. Antisecretory agents reduce the amount of acute mucosal injury from aspirin in part by diminishing pH-dependent trapping.
- Administering NSAIDs parenterally can also increase the risk of ulcer, often without the superficial mucosal damage typically seen with their topical administration. For example, ketorolac tromethamine (Toradol) given daily at an intramuscular dose of 90 mg for five days produced invasive antral ulcers in four of five subjects tested.[2] Two points are important: a drug's systemic action may mediate an ulcer risk, and the absence of acute injury does not guarantee the absence of an ulcer risk.
- Certain NSAIDs, such as indomethacin and the oxicams, enter the enterohepatic circulation, thereby producing high intestinal concentrations of active drug. These NSAIDs that are recirculated cause intestinal damage, resulting in bleeding, perforation, and strictures from ulcers or focal submucosal injury.[3] The enterohepatic circulation of NSAIDs contributes to duodenal mucosal drug exposure and also to gastric mucosal exposure (to the extent of duodenal-gastric reflux).

The relative contributions to the NSAID-induced ulcer risk

resulting from topical action, parenteral delivery through the arterial circulation, and recirculation enterohepatically have not been determined. Each of these routes probably has different pathogenesis with the different NSAID formulations. For example, enteric coating of aspirin prevents pH-dependent trapping in the stomach and reduces acute mucosal damage, but blood levels remain high, and these formulations have not been shown to reduce the risk of ulcer.

Categories of NSAID Mucosal Damage

These drugs induce a spectrum of mucosal damage, but their effects fall into three categories that carry different implications:

- Superficial damage, consisting of petechiae or intramucosal hemorrhages and erosions;
- Silent ulcers found at surveillance endoscopy; and
- Clinical ulcers presenting symptomatically, often with complications.

Pathologists can easily distinguish between erosions and ulcers; erosions are superficial, being confined to the mucosa, whereas ulcers penetrate beyond the mucosal limits. Endoscopists can diagnose an ulcer only when there is obvious depth; ulcers and erosions are often differentiated by size because larger lesions tend to be deeper, but this distinction is arbitrary and sometimes misleading. Depth cannot be used as an absolute criterion because some ulcers are filled with exudate. Therefore, in the absence of perceptible depth, cautious observers currently opt to refer to these endoscopically visualized "ulcers" as "lesions."

A distinction is drawn between clinical ulcers and ulcers found only endoscopically because of the considerable frequency (5% to 25%) with which "ulcers" are found at surveillance endoscopy of persons taking NSAIDs. Most such ulcers remain clinically silent, however, and only a few persons (< 1% to 4%) taking NSAIDs continuously for a year will present with ulcer complications. It is possible that silent and clinical ulcers represent distinct disorders that differ with respect to pathogenic mechanisms and may respond differently to preventive or therapeutic intervention.

How Do NSAIDs Induce Damage?

All NSAIDs share the ability to inhibit the enzyme cyclooxygenase, which is responsible for the conversion of arachidonic acid into prostaglandins. The weight of speculation plus three lines of evidence supports the thesis that ulcers from NSAIDs reflect an inhibition of mucosal prostaglandin production:

- Nonsteroidal anti-inflammatory drugs inhibit mucosal prostaglandin production. It is difficult to quantify the synthesis of mucosal prostaglandin, however. To date, no studies have correlated the degree of inhibition of prostaglandin production and the ulcer risk.
- Immunoneutralizing prostaglandin with specific antibodies also induces ulcers in experimental models,[4] suggesting that prostaglandin deficiency is ulcerogenic.
- Prostaglandin replacement markedly reduces the risk of ulceration from NSAIDs, especially in the gastric mucosa.

Although such lesions in the stomach are dramatically prevented with prostaglandin co-therapy with NSAIDs, standard doses of histamine H_2-receptor blockers are ineffective. Thus, the antisecretory action of prostaglandins does not play an important role because H_2-receptor blockers are more effective antisecretory agents but less effective in preventing NSAID-induced gastric ulceration.

What Critical Role Is Played by Endogenous Prostaglandins?

The ability of the mucosa to withstand sustained insult reflects both defensive and repair capabilities.[5] Defense mechanisms consist of the pre-epithelial elements of mucous and bicarbonate secretion. The mucous gel significantly retards luminal hydrogen ion diffusion, and the thickness of this gel correlates inversely with intracellular pH in the face of luminal acid. Second, epithelial cells have several defensive capabilities: the apical membrane of gastric mucosal cells resists penetration by acid, intrinsic mechanisms involving glutathione and possible heat-shock proteins also resist injury, and several transport mechanisms extrude excess acid and maintain intracellular pH. Last, the maintenance of mucosal blood flow is critical in removing hydrogen ions that do penetrate and in supplying the metabolic substrates necessary for the transport and synthetic functions of the mucosa. Prostaglandins appear to enhance several of these defense mechanisms, and possibly a summation of these effects mediates the enhanced resistance to injury with prostaglandin treatment. Conversely, NSAID treatment would compromise these defenses and predispose to injury by acid-peptic activity or other agents (like bile salts).

Each of these defensive elements contributes to the ability of the mucosa to tolerate insult, but still cell injury frequently occurs and the mucosa is called on to repair damage to restore integrity. When the basement membrane is intact, neighboring epithelial cells slide over to fill in gaps created by cell loss, a process called restitution. Secondary cell replication is enhanced in response to injury. Mucosal wounds, with breaks in the basement membrane, develop when these defensive and epithelial repair mechanisms are overwhelmed. Such wounds are common following the ingestion of high doses of NSAIDs. The healing of these mucosal wounds approximates the phases described in classic wound healing models: the recruitment of inflammatory cells, fibrinoid necrosis, resorption of cellular debris, the formation of granulation tissue, neovascularization, remodeling of the extracellular matrix, and the migration of epithelial cells from the margins of the wound. Ultimately, clinical ulcer disease develops only when these wound healing mechanisms fail. A failure of angiogenesis may be a critical, rate-limiting step in ulcers that fail to heal.

No clear role for endogenous prostaglandins in these repair mechanisms has been defined. Some evidence suggests that NSAIDs inhibit cell replication in the ulcer margin, but little is known about factors that retard the repair and wound healing process, despite the central role the failure of these mechanisms plays in ulcer formation.

NSAID Ulcers: Failed Adaptation

Many people take NSAIDs, and yet ulcers develop in only a few. Acute mucosal damage occurs in the majority of persons soon after starting aspirin therapy, yet recovery is seen in many even during sustained exposure. Thus, it appears that some adaptation occurs, at least for superficial injuries.[6] In a myocardial infarction prevention study, subjects were randomly assigned to take 1 gram of aspirin or placebo daily. The risk of ulcer was sustained over the four-year study

period.[7] Thus, the large majority of persons tolerate sustained aspirin or NSAID use without clinical ulcer disease developing; only a small percentage fail to adapt to this suppression of mucosal prostaglandin production. The pathophysiologic mechanisms that differentiate the subjects who tolerate sustained NSAID exposure from those in whom clinical ulceration develops are not known. The initial superficial damage is widespread, but ulcers develop focally. One can only speculate that these differences reflect elevated nocturnal acid secretion, failed primary mucosal defense mechanisms, failed restitution or cell replication, or failed wound healing. The understanding of NSAID ulceration is eclipsed by what is not known.

Common Forms of Peptic Ulcer

Because of the defense and repair mechanisms noted earlier, normal gastric mucosa and duodenal mucosa have a remarkable ability to resist injury from the acid-peptic activity in gastric secretions. In fact, peptic ulcers do not occur unless these defense mechanisms are disrupted by exogenous factors. Ulcers due to NSAID use are one common form of ulcer. The other common form is associated with *Helicobacter pylori* and the antral gastritis that develops in infected persons. Both NSAIDs and *H pylori* presumably cause ulcers by disrupting mucosal defense and repair mechanisms. Both forms of ulcer are still appropriately called "peptic" ulcers, however, because there is also a critical dependence on a sufficient level of acid-peptic activity in gastric secretions.[5] Controversy still exists regarding the role of *H pylori* in peptic ulcers. Causality has been difficult to assess in large part because the background rates of *H pylori* infection in the asymptomatic "normal" population are high. The eradication of *H pylori*, however, is associated with a pronounced reduction in the tendency for ulcers to recur.[8]

The relation between *H pylori* and NSAID ulcers is complex and unresolved. About half of clinical ulceration with NSAIDs occurs in the absence of *H pylori* or antral gastritis—the "virgin NSAID ulcer." On the other hand, NSAIDs clearly exacerbate an underlying ulcer diathesis. A large grey zone exists regarding whether the presence of *H pylori* or antral gastritis per se predisposes to NSAID ulceration. This predisposition, if established, would imply that eradicating *H pylori*, even from persons without an ulcer history, might significantly decrease the risk of NSAID ulceration. No data support this thesis at present, however.

Clinical Perspectives

Damage to the esophagus has not been widely recognized, although it is becoming increasingly clear that NSAIDs exacerbate acid-peptic injury to the esophagus.[1,9] Patients with esophageal symptoms certainly deserve a careful history to exclude NSAID consumption and a trial off NSAIDs. Of interest, a substantial number of patients (about 25% in one study)[9] denied taking NSAIDs, although it was later established on testing of platelet aggregation or blood aspirin concentrations.

The consumption of NSAIDs is also associated with a widespread disruption of mucosal integrity in the intestine. Bacteria are involved in secondary damage, just as acid and pepsin are involved in secondary damage to the gastroduodenal mucosa. Injury is common, but the clinical effects appear infrequent. An important factor is that the risk appears to hold only for those NSAIDs that undergo enterohepatic recirculation, suggesting the importance of luminal exposure or high local concentrations. In the colon, NSAIDs can precipitate bleeding from preexisting lesions, supporting the practice of studying patients with occult gastrointestinal bleeding while taking NSAIDs. Their use may exacerbate inflammatory bowel disease.

The risk of ulcers from NSAIDs creates anxiety in this era of cost-conscious, litigation-phobic medicine. It would be inappropriate to place all patients taking NSAIDs on preventive, expensive antiulcer therapy. Emphasis should be placed on identifying factors that might predict ulcer risk, such as age, previous ulcer history, and co-therapy with steroids, as considered by Babb.[1] Are these risk factors helpful in identifying those who really deserve preventive therapy? Does preventive therapy substantially reduce the risk of complications from clinical ulceration? It is clear that misoprostol prevents silent ulceration in the stomach and duodenum, and the use of H_2-receptor blockers prevents silent duodenal ulceration, but how many patients are kept out of emergency departments by these interventions? The answers to these questions remain unclear.

Ulcers occurring as a result of NSAID therapy are generally easy to treat if the therapy can be stopped. Unless the ulcer is exceptionally large, any treatment will work well. When the physician and the patient decide that the benefits of NSAID therapy warrant continuation, however, the treatment of the ulcer becomes more challenging. Few controlled clinical trials include enough patients who continued taking NSAIDs during ulcer treatment to arrive at interpretable conclusions. No data support the use of antacids or sucralfate in the face of continued NSAID consumption. The efficacy of H_2-receptor blockers appears to be diminished, particularly with healing gastric ulcers.[10,11] The healing efficacy of omeprazole for gastric ulcers may not be compromised by continued NSAID use, but the small number of subjects studied demands additional trials before this approach can be recommended.[10]

The healing and prevention of NSAID ulcers reflect different processes; although misoprostol use effectively prevents silent ulcers found endoscopically, its comparative efficacy for ulcer healing remains to be firmly established. Therapy with prostaglandins underwent trials for non-NSAID ulcers, with the hope that combining "cytoprotective" with antisecretory actions would be uniquely effective. This proved not to be so. Prostaglandins healed ulcers, but only with an efficacy predicted by their antisecretory actions, which are generally of lesser magnitude than those produced by H_2-receptor blockers.[7] Misoprostol does appear to enhance the healing of aspirin-associated silent ulcers with greater efficacy than placebo, but healing was only about 70% at four weeks, with no further increase after eight weeks of therapy.[12] Until more data are presented, misoprostol cannot be considered acceptable therapy for healing NSAID ulcers. One can only speculate that prostaglandins appear more effective than H_2 blockers for preventing NSAID ulcers. This difference may reflect prostaglandins acting on normal glandular structures and blood vessels to enhance resistance to injury—for example, enhanced mucous and bicarbonate secretion and blood flow—and therefore to prevent ulceration. In contrast, prostaglandins do not appear to enhance the wound healing process of ulcers in which the rate-limiting step appears to be the ingrowth of new blood vessels into granulation tissue. Much mystery persists regarding NSAID

ulceration, and many interesting questions warrant vigorous study.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

'What Kind of Work Do You Do?'

To the Editor: The Lessons From the Practice by Dana Hoch, MD, in the June issue[1] rekindled memories of comparable conversations with patients. In "The Craft," a man with terminal cancer momentarily lost his profound depression when asked, "What kind of work do you do?"

It has long been the experience of seasoned practitioners of occupational medicine that irrespective of a patient's disease, injury, or resulting disability, inquiry into his or her lifetime work will bring about an instant change in demeanor. The person brightens suddenly and will begin a cogent dissertation on the years of devotion to a particular occupation. There is pride in the work accomplished, and this feeling is imparted with a zest completely antipodal to the despair accompanying the clinical disorder.

This form of revelation and temporary return to cheer has been used over the years in the teaching of medical students. While the disease process or the illness residua might be paramount in the student's case presentation, the dissecting out of the occupational history gives emphasis to the neophyte physician of the centrality of work to all of us and of the innumerable connections between labor and health.

For a return to the patient's view of the premorbid state and an insight into the person who was, do ask, as did Dr Hoch, "What kind of work do you do?"

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REFERENCE

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Cancer Screening in Women

To the Editor: In the article, "Cancer Screening in Older Adults," in the May 1992 issue,[1] there is a statement that a 65-year-old woman at average risk who has previously been adequately screened for cervical cancer with Papanicolaou smears and who is then screened for an additional four examinations, every three years for at least 12 years, would decrease her chance of death from cervical cancer by about 18 in 10,000. The costs incurred are stated to be $52,241 per year of life saved. This is a puzzle to me, as the cost of an average gynecologic examination along with a Pap smear interpretation by a pathologist does not approach the amount quoted. I would like to know how this figure was derived; if it was calculated on the basis of the cost of an average gynecologic examination, along with the cost of an average Pap smear in our area, I would say that this perhaps approaches $125, possibly $225 at the very most. Perhaps the comma was out of place in the printing of the article?

I am also curious why there was no mention made of endometrial cancer in this article. Certainly the routine gynecologic examination can detect enlargement of the uterus that might signify a problem in a woman over the age of 65. Also, although the statement is made that there is no evidence that such detection leads to an improved clinical result from the standpoint of cervical cancer screening, uterine and ovarian enlargement in a postmenopausal woman do warrant further evaluation, to include possible pelvic ultrasound.

The main reason I am writing is that I think it would be a disservice to older women to ignore a relatively easy, inexpensive means of screening for these common cancers in women. It is my strong belief that yearly pelvic examination, or at least bimanual examination, should be done on all women over the age of 65. At that time, a rectal examination is also easily done, to include the Hemoccult test, which, although certainly not a perfect test, is also easy and inexpensive to do.

I do cervical cancer screening such as Pap smears as is recommended by the consensus group and think that after age 65, this can be individualized and often can be done less frequently on the basis of history.

I hope that there was truly a mistake made in the calculation of costs per year of life saved regarding cervical cancer screening, as the Pap smear is an important tool to offer to all women as part of their health maintenance screening.

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1. Walsh JME: Cancer screening in older adults. West J Med 1992 May; 156:495-500

* * *

Dr Walsh Responds

To the Editor: Dr Senter addresses two important issues, the cost-effectiveness of screening for cervical cancer and the use of the bimanual examination in screening for endometrial cancer.

The cost (per year of life saved from screening for cervical cancer in a 65-year-old-woman at average risk) of $52,241 was calculated by Eddy[1] and assumed a charge of $75 for a pelvic examination and Pap smear. The cost-effectiveness of screening for cervical cancer, however, involves more than simply the cost of a single Pap smear. Cost involves only the cost of a single examination to the person screened, whereas cost-effectiveness is a public health issue. When a disease is uncommon, as is cervical cancer in older women, many persons must be screened to detect a single case of cervical cancer. If the incidence of cervical cancer in women aged 70 to 74 is 12 per 100,000, 8,333 women must be screened to detect a single case. Thus 8,332 of these women are paying for a screening examination that they may not need. Other factors that contribute to the cost-effectiveness calculation include the false-positive rate of screening (necessitating repeat Pap smears and possibly colposcopy and endocervical biopsy), expected savings from finding disease in early stages (when treatment costs are lower), and expected sav-

ings from lower costs for terminal care. All these factors contribute to the cost of $52,241 per year of life saved.

Although endometrial cancer is more common in older women, it is still an uncommon disease. Dr Senter suggests using the bimanual examination as a screening technique. Koss and colleagues screened a cohort of 2,586 asymptomatic women for endometrial cancer over a 3½-year period (68% of the women underwent more than one screening). All women underwent direct endometrial biopsy and bimanual pelvic examination. Overall, 17 cases of occult uterine carcinoma were detected. Of these, only 2 had enlarged uteri.[3] Thus, in this cohort the sensitivity of screening asymptomatic women for endometrial cancer using bimanual examination was only 12%. A test with a sensitivity of only 12% is not appropriate for use in mass screening. Because 80% of women with endometrial cancer present with abnormal bleeding, however, teaching women to report postmenopausal bleeding is an important preventive strategy.[2]

Certainly decisions about screening for cancer in the elderly should be individualized, and clinicians must weigh the risks and benefits for each patient. Routine screening, however, for rare diseases using screening tests that have low sensitivities may not be the most prudent use of preventive resources.

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Exaggerated Threat of Childhood Lead Poisoning in California—Epidemic by Edict

To the Editor: California children were previously considered to be at low risk for lead poisoning compared with children in Eastern states such as Massachusetts and Maryland, where old, deteriorated housing with leaded paint is presumably more common. In 1989 the California Department of Health Services (CDHS) reported on blood lead levels in infants and children younger than 6 years living in Oakland and Los Angeles inner-city census tracts in old housing and found levels of 1.21 μmol per liter or higher (≥25 μg per dl) in 1.3% and levels of 0.72 μmol per liter or higher (≥15 μg per dl) in 19% to 20% of children tested.[1] A blood level of 1.21 μmol per liter or higher was then considered the "action level" for intervention, and a level of 0.72 μmol per liter or higher was chosen for testing because of a perceived probability that the level considered cause for concern would be decreased to within this range by the Centers for Disease Control (CDC). In October 1991, the CDC lowered the levels considered abnormal to 0.48 μmol per liter or higher (≥10 μg per dl),[2] thus increasing by 10-fold to 15-fold the number of children considered lead poisoned. The CDHS recently reported that according to 1987 and 1988 surveys, 67% of children tested in Oakland had lead levels exceeding this new 0.48 μmol per liter or higher action level.[3] Not stated was that the finger-stick, capillary method used in this study, described as "extremely inaccurate even when proper precautions were taken to avoid contamination," resulted in a false-positive rate of more than 50%.[1(p19)]

Subsequent to the 1989 CDHS report, evidence showed that both prevalence and risk of low blood lead levels in children have been greatly exaggerated. Because of a lawsuit brought by Matthews against Coye and settled out of court, the CDHS agreed to mandate blood lead screening, through public programs, for children in low socioeconomic groups; such children would be expected to have higher lead levels than the general population. To date, data on this group indicate blood lead levels are much lower than reported in the earlier Oakland study. Of 1,200 children tested by the San Francisco Health Department, 8.5% had blood lead levels of 0.48 μmol per liter or higher,[4] and of more than 1,000 children tested at Children's Hospital, Oakland, 14.6% had levels of 0.48 μmol per liter or higher (Patricia Chase, MD, unpublished data, 1992). Most, though not all, of the children tested at Children's Hospital were in public programs; some were higher-income children tested at their parents' request. Of 136 children in a private pediatric practice in East Oakland—mainly African-American children receiving Medi-Cal benefits—7.4% had levels of 0.48 μmol per liter or higher (Raymond Davis, MD, unpublished data, 1992). Recent childhood lead testing, using more accurate test methods and venous blood, indicated that the prevalence of blood lead levels of 0.48 μmol per liter or higher in Oakland is five to nine times lower than that reported by the CDHS, even though the groups tested were of low socioeconomic status. The 1989 CDHS report apparently exaggerated the prevalence of elevated blood lead levels in Oakland by selecting a very high risk group that was not representative of the area's general population (or even of children receiving public assistance) and by using seriously flawed testing methods.

Similarly, in the state of Washington, Konig and Robertson found that of 271 high-risk toddlers, only 6.3% had blood lead levels of 0.48 μmol per liter or higher, indicating that the data presented by the Environmental Defense Fund purporting a 40% prevalence at these levels were "severely flawed and grossly exaggerated."[5(p13)]

Similar charges of impropriety and poor methodology have been leveled against the leading United States protagonist of low lead levels damage.[6,7] In view of other more urgent health needs of our children, legislators and health officials in California and nationwide should be wary of allocating major funding to mass lead-screening programs until issues of misleading information, questionable statistical manipulation, and flawed data have been resolved.

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Another Health Food Hazard—γ-Hydroxybutyrate-induced Seizures

To THE EDITOR: We report another case of γ-hydroxybutyrate (GHB)-induced seizure in a young amateur body builder, who obtained the drug from a health food store.

Report of a Case

The patient, a 40-year-old man, suffered a 30-second tonic-clonic major motor seizure without a previous history of epilepsy, head injury, or substance abuse. He had been using 1 to 2 tsp per day (2.5 to 5.0 grams) of GHB, but on the day of the seizure took a larger dose (about 115 mg per kg of body weight) 20 minutes before onset of the seizure. Extensive neurologic and laboratory study results were negative. Off GHB for 30 months, he has remained seizure-free without treatment.

In reporting this case to the California Department of Public Health, we learned of other cases, recently reported in this journal.[1] The drug has been removed from the shelves of health food stores and fitness centers, and it is now illegal to promote and distribute GHB in California. As neurologists, we were intrigued that this drug, which has been used in animals as a model for experimental epilepsy in doses of 260 mg per kg of body weight,[2] was available in health food stores. The other actions of GHB in narcolepsy and its effect on muscle metabolism are well described.[3] As alternative sources for γ-hydroxybutyrate and other types of substances may develop, both physicians and patients should be aware of the hazards of health food store pharmacotherapy.

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Licensing of Tissue Banks in California

To THE EDITOR: A new law has recently been enacted in California that requires all tissue banks to be licensed by July 1, 1992 (Assembly Bill 2209, Speier, chapter 801 of Statutes of 1991, Health and Safety Code, Division 2, chapter 4.1 [commencing with section 1640]). It applies to all persons or entities who or that collect, process, store, or distribute human tissue for transplantation and includes physicians who process or store tissues such as semen, bone, and others in their office for use in treating patients.

This new law defines "tissue" as any human cell, group of cells, tissue, or organ including the cornea, sclera, or vitreous humor and other segment of, or the whole eye, bones, skin, arteries, semen, blood, or fluids, and any other portion of a human body. Six situations are exempt from licensure:

- The collection, processing, storage, or distribution of human whole blood or its derivatives by licensed blood banks, blood collection centers, and blood bank depositories (transfusion services).
- The collection, processing, storage, or distribution of tissue for autopsy, biopsy, training, education, or for other medical or scientific research or investigation, where transplantation of the tissue is not intended or reasonably foreseeable.
- The collection of a tissue by individual physicians and surgeons from their patients or the implantation of tissue by physicians and surgeons into their patients. This exemption shall not be interpreted to apply to any processing or storage of the tissue.
- The collection, processing, storage, or distribution of fetal tissue or tissue derived from a human embryo or fetus.
- The collection, processing, storage, or distribution by an organ procurement organization, as defined by Title 42 of the Code of Federal Regulations.
- The storage of prepackaged, freeze-dried bone by a general acute care hospital.

For further information and applications for tissue bank licensure, physicians should contact Ron Harkey, Examiner, Laboratory Field Services, at 2151 Berkeley Wy, Rm 602, Berkeley, CA 94704, or by telephone at (510) 540-2488.

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Pulse Oximeter Versus Electrocardiogram

To THE EDITOR: I do not agree with Kevin K. Tremper, PhD, MD, that "Today, if given the choice of one monitor, most anesthesiologists would quickly choose the pulse oximeter over the electrocardiogram (ECG) or noninvasive blood pressure devices."[1] Anesthesiologists have several ways of monitoring ventilation and oxygenation by inspecting the patient. These include noting the chest movement and color of the skin and mucous membranes. No amount of inspection, however, will reveal cardiac dysrhythmias and ST segment changes that only the ECG can show.

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1. Tremper KK: Noninvasive monitoring of oxygenation and ventilation—40 years in development. West J Med 1992 Jun; 156:662-663

* * *

Dr Tremper Responds

To THE EDITOR: In response to Dr Cozen's letter, he may be right. The only way to know would be to do a survey. I do not agree that it is necessarily easy to evaluate oxygenation by inspection. Comroe and Botelho showed in early studies that inspection was often misleading, especially in the presence of anemia.[1] It requires approximately 5 grams of circulating reduced hemoglobin to produce cyanosis. If a patient has a hematocrit of 27% (9 grams per dl) the Pa_{O_2} would have to be below 25 mm of mercury before cyanosis would be detectable. In most patients we care for, a standard manual blood pressure cuff and palpation can provide an assessment of perfusion. An ECG will provide information in addition to the pulse rate provided by the pulse oximeter. In actuality, the ECG does not ensure there is a pulse. Analysis of the ST

segment is a recent addition to routine monitoring that may indeed prove useful in some patients, so we have equipped all our operating rooms with this capability. I still stand by my opinion and agree that it is just my opinion.

To settle this issue, I have conducted an unbiased survey of anesthesiology faculty from a well-known university medical center in the Midwest. Of the 48 faculty surveyed, the following results were found:

Pulse oximeter	34
NIBP*	4
ECG	2
No response	8

I rest my case.

*Noninvasive blood pressure monitoring, if no manual blood pressure.

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Discounting Our Future

To the Editor: I read the commentary "On Sale: Future Health Care—The Paradox of Discounting"[1] with interest and alarm. The concept of discounting, nicely graphed at both 5% and 10% to 40 years, is informative yet misleading. There is no discounting percentage that will stay constant for 40 years. These mathematical concepts that will be used by health care economists are abstract theories out of touch with the human condition and the nature of societies.

Rather than use discount rates of 5% or 10%, why not use terms like shortsighted, living for the present, mortgaging your future and your children's future to more accurately portray the real issues? We in the United States are already reaping the "rewards" of discounting the future in health, education, and the general well-being of society. As our society is in the process of collapse, people are living more for the present at the expense of the future. In actuality, the discounting rate (whatever it actually is) is increasing alarmingly. One wonders whether the discount rate stayed stable over the last 40 years of the Roman Empire.

Sarcasm aside, neat formulas to be used by economists on which crucial health care decisions will be based are out of touch with reality and are an extreme disservice to the field of medicine and society as a whole.

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1. Ganiats TG: On sale: Future health care—The paradox of discounting. West J Med 1992 May; 156:550-553

* * *

Dr Ganiats Responds

To the Editor: I appreciate the wit Dr Coren applies in his letter regarding the recent article on discounting.[1] As he correctly points out, the current practice of discounting can be misleading. For example, there is little evidence that the discount rate remains constant over a 40-year period; yet, it is common practice to assume a constant discount rate in health policy research. As discussed in the article, such a practice can have a major effect on health policy decisions. Apparently it can also lead to letters to the editor appropriately laced with sarcasm.

The health care system is currently in a cost crisis, and some authors fear the collapse of the system as we know it by the end of the decade. I do not think discounting is the cause of this collapse, any more than I would attribute the fall of the Roman Empire, as referenced by Dr Coren, to the discount rate. Still, the problems presented by inappropriate discounting are potentially substantial, and this justifies further work in the science of discounting. Some of the key questions were listed in the last section of my article. The basic issue is not whether we should discount, but how we should discount. The answer lies in our patients' actual preferences. Many investigators, including our team here at the University of California, San Diego, continue to work on these issues. I agree with Dr Coren that we should make sure the discount rate stays in touch with reality. If not, then we should abandon the use of discounting in favor of a more appropriate model.

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Meta-analyses Revisited

To the Editor: We wish to thank Peter L. Havens, MD, for his editorial ("Meta-analysis Redux: Steroids and Meningitis Revisited")[1] concerning our recent meta-analysis.[2] Although his points were well expressed, the reader may be served by a presentation of views different from Dr Havens regarding two areas that he addressed.

In his editorial, Dr Havens cites a retrospective review of 97 children with pneumococcal meningitis performed by Kennedy, Hoyt, and McCracken.[3] Dr Havens summarizes the study by stating that there were "no statistically significant differences in the neurologic or audiologic sequelae of patients treated with dexamethasone compared with those not so treated."[1] It is true that no significant difference for hearing impairment ($P = .14$) or long-term adverse neurologic outcome ($P = .18$) existed in the study.[3] Kennedy and co-workers also included a calculation of total adverse outcome, which is not mentioned in the editorial by Dr Havens. This calculation, combining audiologic and neurologic sequelae, did reach significance ($P = .033$). The authors stated that it was their belief that corticosteroid therapy is beneficial in infants and children with pneumococcal meningitis. Dr Havens's reference to data from this study may lead readers to conclude that corticosteroid therapy in pneumococcal meningitis is a "bust." The converse, however, seems to be true.

In addition, Dr Havens seeks to compare results between children treated with different antibiotics, specifically those treated with cephalosporins,[4-6] and those treated with ampicillin and chloramphenicol.[7] His concern is that patients treated with cephalosporins experience a greater incidence of neurologic sequelae than those treated with ampicillin or chloramphenicol. While it certainly is important to know if a difference in efficacy exists between antimicrobial therapies,

the data presented by Dr Havens have an important source of bias; the mean follow-up time for those treated with chloramphenicol and ampicillin is much longer than for those treated with cephalosporins. In four studies using cephalosporins, final follow-up examinations were done at 1 year after discharge,[4] 6 weeks after discharge,[5] and 5 to 25 months after discharge (mean 15.5 months).[6] The mean follow-up interval for those treated with ampicillin and chloramphenicol was 8.9 years.[7] This difference in follow-up for those treated with cephalosporins and those treated with ampicillin and chloramphenicol makes conclusions difficult to reach because of the decrease in sequelae that tends to occur with time. Pomeroy and associates show a temporal difference in neurologic abnormalities between one month after meningitis (37% with abnormalities) and the last examination at a mean of 8.9 years (14% with abnormalities).[7]

Quantitative reviews of the literature are difficult to do primarily because of the myriad ways in which data can be analyzed. In our meta-analysis we sought to reduce bias by defining strict standards for study inclusion and by analyzing specific outcomes. It is our belief, then, that the data from our analysis do show a beneficial effect of dexamethasone in addition to antimicrobial therapy for children with bacterial meningitis.

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Lessons From the Practice

A Suitcase Full of Pills

RICHARD E. WALTMAN, MD, *Tacoma, Washington*

In 1978 I worked at the medical school of Ben-Gurion University in Beersheva, Israel. As part of my duties I traveled each week to a rather remote town to run an evening clinic. Before the clinic I had dinner in the town's only restaurant. After a few visits, Nathan, the owner-cook-waiter of this establishment asked me if I could sign his disability papers every month and thereby save him a six-hour, back-and-forth bus trip to the hospital. I told him that if the papers were in order I would be happy to sign them, and because they were, I did.

Then he asked another question: would I also be willing to renew his medications for him. Let me see them, I said, and probably I would.

To my dismay he returned with a large suitcase. Inside the suitcase were multiple bottles containing all sorts of medications. We sorted them out on the table; with that collection this man could have opened a pharmacy. He had a wide variety, and some were over ten years old. But what was most striking was that none of the bottles were open.

I asked him about that. "I don't take any of this. Pills are bad for you," he said.

"But you get them filled," I said. "I know they're free with your insurance, but you do have to pay the service charge. Why do you get them if you don't take them?"

He smiled. "My doctors are wonderful," he said, "and doctors like to give you pills. Every time I see my doctors they give me pills. If I didn't take them it would hurt their feelings."

I couldn't find any medication he really needed, particularly since he hadn't been taking any. I explained to him that it wouldn't hurt my feelings at all if he didn't take the pills, and he was pleased to hear it. I carted all the bottles back to the hospital pharmacy to see if at least some could be used. And I thought about his clinic chart, which probably had comments from his physicians about how many medications he was taking and how fond of taking medications he was. I was certain that "polypharmacy" was listed as a problem.

I had dinner in his restaurant every Wednesday night for the next six months. Although he did have a permanent disability from a previous injury, he never took a pill during that time and did very well without them. He always enjoyed introducing me to customers as the doctor who took all his pills away.

Recently I was preparing to give antibiotics to a patient with an upper respiratory tract infection. I felt she really didn't need them but would probably want them. She took me by surprise when she asked if she really had to take them. If it was all right with me, she explained, she would rather try a few days without them. I agreed, told her to drink lots of fluids and get plenty of rest. When we called her a few days later she was much better, and she told my nurse she hoped she hadn't hurt my feelings and how happy she was to have a doctor who didn't "push pills."

It was a good reminder, and it brought back memories of Nathan. I had forgotten what he taught me along with the good dinners he gave me: Before we complain about our patients always wanting us to give them medications, we should make certain that when we write a prescription we are not meeting our own needs instead of theirs.

* * *

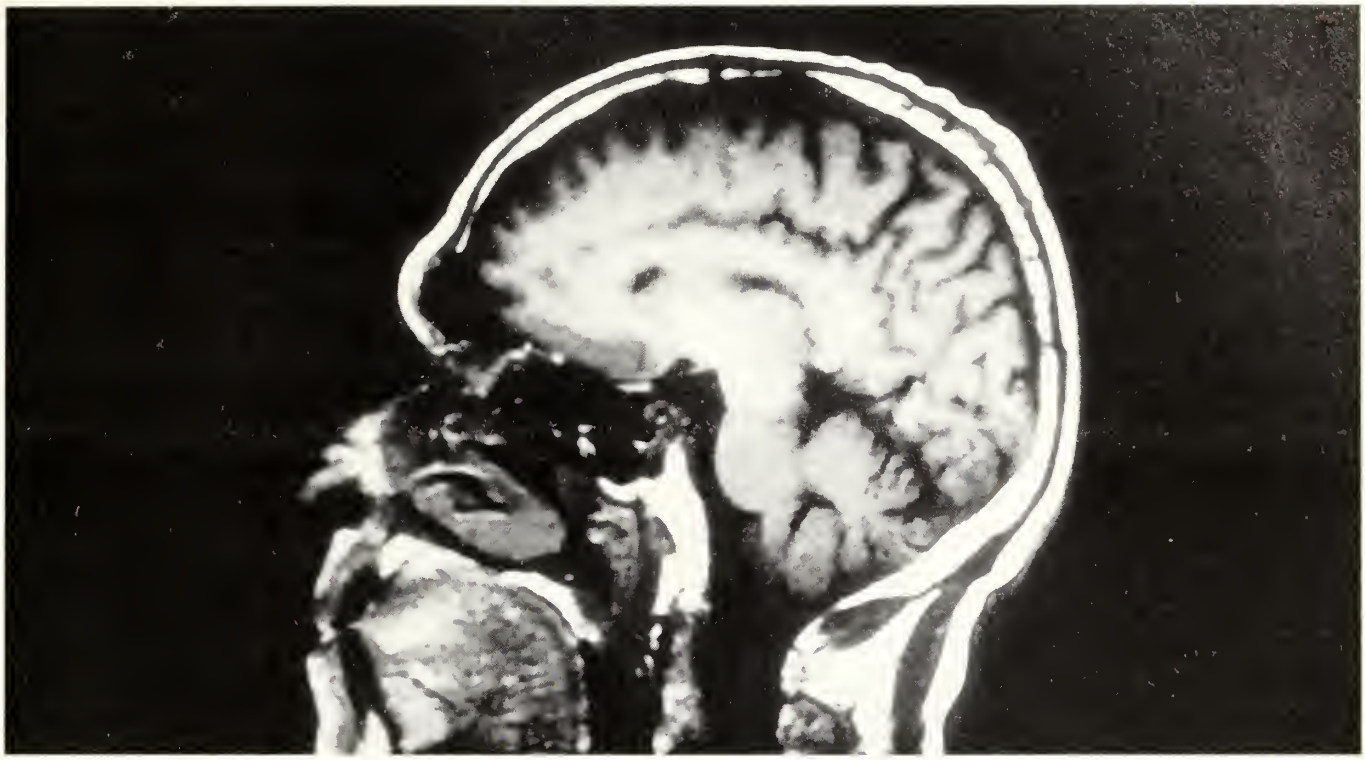
"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Waltman RE: A suitcase full of pills. West J Med 1992 Oct; 157:474)

From the Allenmore Medical Center, Tacoma, Washington.
Reprint requests to Richard E. Waltman, MD, Allenmore Medical Center, Suite A-244, S 19th and Union, Tacoma, WA 98405.

YOU DON'T HAVE TO BE A BRAIN SURGEON TO APPRECIATE OUR NEUROSCIENCE CENTER, BUT IT HELPS.



When we asked Dr. Cully Cobb why he routinely performs neurosurgery at Sutter General Hospital, he explained, "Neurosurgery has become very complex. Multiple specialities overlap and are interdependent. To provide optimal care, a physician needs a full range of services. Sutter General is one of the few hospitals that offer that kind of support." In fact, Sutter Neuroscience Center at Sutter General Hospital is the only private facility in the region that offers such a wide array in the way of neurology services. Interventional neuroradiology, angiography and neuropathology are available, along with comprehensive epilepsy services and advanced neurodiagnostics, including intraoperative studies. The six-bed Neuro Observation Unit lets physicians monitor patients' neurologic status, including EEG and intracranial pressure, around the clock. The nursing staff is specially trained in neuroscience. And neuro rehabilitation specialists provide ongoing care for patients. As Dr. Cobb puts it, "Many centers emphasize only one area. At Sutter General, there's excellence in every aspect of neurosurgical care. The equipment is top-notch. The facilities are excellent. There are superb physicians. And the operating room and neuroscience staff is outstanding." Then he adds, "Neurosurgery is like a gigantic jigsaw puzzle. If one part is missing, it's a disaster. At Sutter General, all the parts are there. And they work together beautifully." For more information about available services, call Sutter Neuroscience Center at Sutter General Hospital in Sacramento, (916) 733-3049.

Cully Cobb, M.D.

Sutter Neuroscience Center
SUTTER GENERAL HOSPITAL

(Continued from Page 419)

October 19-22—**17th Annual Pediatrics for the Practitioner.** Long Beach Memorial at Mauna Kea Beach Hotel, Kamuela, Hawaii. Contact: Eunice Larson, MD, (310) 595-3422.

October 22-26—**Lactation Educator Training Program.** UCLA at St Agnes Medical Center, Fresno. Thurs-Mon. 22.5 hrs. $740. Contact: UCLA Extension.

January 26-30—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Hyatt Regency, La Jolla. Tues-Sat. Contact: Center for Child Protection, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4950.

February 15-17—**Pediatrics Update.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

February 26-28—**Current Concepts in Pediatric Medicine: 1993.** Children's Hospital San Diego and American Academy of Pediatrics at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Continuing Education, 8001 Frost St, San Diego 92123. (619) 576-4072.

PSYCHIATRY

November 5-7—**Addiction Medicine: 1992 Review Course and Workshops.** California Society of Addiction Medicine and American Society of Addiction Medicine at Ramada Renaissance Hotel, Long Beach. Thurs-Sat. 20 hrs. $350. Contact: CSAM, 3803 Broadway, Oakland 94611. (510) 428-9091.

November 13-15—**38th Annual Group Therapy Symposium.** UCSF at Holiday Inn Union Square, San Francisco. Fri-Sun. 21 hrs. $245. Contact: UCSF.

January 24-29—**19th Annual Midwinter Program for Psychiatrists: Special Focus on Hysteria.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 12-14—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Catamaran Hotel, San Diego. Fri-Sun. Contact: UCSD.

February 27—**Sleep Apnea: New Insights into Pathophysiology and Treatment.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

RADIOLOGY

October 24-25—**Musculoskeletal Imaging.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 26-30—**17th Annual Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25.25 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 29-November 1—**Current Concepts of Magnetic Resonance.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 19.5 hrs. $450-$550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 30-November 1—**12th Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16.5 hrs. $350. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

November 2-6—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Mon-Fri. 15 hrs. $400. Contact: UCSD.

November 13-15—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 28-January 2—**Year End Review of Imaging and Intervention.** UCSD at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Sat. 25 hrs. $550-$595. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 15-17—**45th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.75 hrs. $125-$450. Contact: LARS, MWRC, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078.

January 16-17—**Interventional Radiology Update.** Stanford University at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 7.5 hrs. $200-$250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 18-20—**Neuroradiology Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 17.5 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 21-24—**Breast Imaging Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 17.25 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 15-19—**Diagnostic Imaging Update: Mammography, MRI, Body Imaging, Neuroradiology, Pediatrics.** Stanford University Medical Center at Ritz-Carlton, Palm Beach. Mon-Fri. 23.75 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 22-26—**Diagnostic Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Kapalua Bay, Maui, Hawaii. Mon-Fri. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 8-12—**8th Annual San Diego Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel Del Coronado, San Diego. Mon-Fri. 29 hrs. $595. Contact: Dawne Ryals, PO Box 1925, Roswell 30077-1925. (404) 641-9773.

March 10-12—**13th Annual Radiation, Oncology, Biology & Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: Crest Organization (415) 595-2704.

SURGERY

October 16-18—**Hip and Knee Reconstructive Surgery: 1992.** UCLA at Westin Hills Resort, Rancho Mirage. Fri-Sun. 14 hrs. $595. Contact: UCLA Extension.

October 31-November 7—**14th International Seminar on Operative Arthroscopy.** UCLA at Maui Marriott, Maui, Hawaii. Sun-Sat. 36 hrs. $1,045. Contact: UCLA Extension.

January 8-9—**15th Annual Postgraduate Course: What's New in General Surgery.** UCD at Hyatt Regency, Sacramento. Fri-Sat. Contact: UCD.

January 24-29—**16th Annual Postgraduate Assembly in Surgery.** UCSD at Doubletree Hotel, Horton Plaza, San Diego. Sun-Fri. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

December 24-29—**Advances in Medicine '92.** Hawaii Medical Association at Kaanapali Beach, Maui, Hawaii. Fri-Wed. 16 hrs. $450. Contact: Joe Harrison, MD, PO Box 833, Makawao, HI 96768. (808) 878-7657.

February 22-26—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

March 26-April 4—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. 1½ wks. Contact: UCLA Extension.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

Advances in Clinical Rheumatology & Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

(Continued on Page 478)

SEMINARS IN OBSTETRICS AND GYNECOLOGY

In

Las Vegas

Presented by

GYN CME FUND

"PERINATAL MEDICINE"
November 14–15, 1992

Saturday, November 14, 1992
7:00 a.m. **Registration & Breakfast**
7:30–8:30 **"Preconception Counseling"** – Dr. Robert Resnik
8:30–9:30 **"Heart Disease in Pregnancy"** – Dr. Stephen Clark
9:30–10:30 **"Fetal Assessment"** – Dr. Jeffrey Lipshitz
10:30–11:30 **"Antepartum Fetal Surveillance of the Postdated Pregnancy"** – Dr. Jeffrey Phelan
11:30–12:30 **"The Role of Lupus Anticoagulant and Anticardiolipin Antibodies in Reproductive Loss"** – Dr. Resnik

Sunday, November 15, 1992
7:00 a.m. **Registration & Breakfast**
7:30–8:30 **"Terbutaline Pump Therapy"** – Dr. Phelan
8:30–9:30 **"Managing Complications of Severe Pregnancy Induced Hypertension"** – Dr. Clark
9:30–10:30 **"The Evaluation and Management of the Patient with Intrauterine Growth Retardation"** – Dr. Resnik
10:30–11:30 **"Role of Amnioinfusion"** – Dr. Phelan
11:30–12:30 **"Management of the Post-Partum Hemorrhage"** – Dr. Clark

"REPRODUCTIVE ENDOCRINOLOGY"
February 6-7, 1993

Saturday, February 6, 1993
7:00 a.m. **Registration & Breakfast**
7:30–8:30 **"The Future of GYN"** – Dr. Alan DeCherney
8:30–9:30 **"Pathophysiology of Adhesion Formation and Treatment at Pelviscopy"** – Dr. Michael Diamond
9:30–10:30 **"RU - 486"** – Dr. DeCherney
10:30–11:30 **"Intrauterine Insemination"** – Dr. Andrew Friedman
11:30–12:30 **"Endocrine Aspects of Menopause"** - Dr. DeCherney

Sunday, February 7, 1993
7:00 a.m. **Registration & Breakfast**
7:30–8:30 **"Modern Diagnosis of Ectopic Pregnancy"** – Dr. Bruce Shapiro
8:30–9:30 **"Surgical Treatment of Ectopic Pregnancy"** – Dr. Diamond
9:30–10:30 **"Distal Tubal Disease; IVF vs. Surgery"** – Dr. Friedman
10:30–11:30 **"GNRH Use in Management of Uterine Myomata and Endometriosis"** – Dr. Friedman
11:30–12:30 **"Hysteroscopic Treatment of Intrauterine Lesions"** – Dr. Diamond

"CONTROVERSIES IN OBSTETRICAL MANAGEMENT"
July 17-18, 1993

Saturday, July 17, 1993
7:00 a.m. **Registration & Breakfast**
7:30–8:30 **"Fetal Assessment: Which Test is Best?"** – Dr. Jeffrey Lipshitz
8:30–9:30 **"Timing and Mechanisms of Perinatal Neurological Injury"** – Dr. Barry S. Schifrin
9:30–10:30 **"Twins"** – Dr. Thomas J. Benedetti
10:30–11:30 **"Cervical Cerclage vs. Preterm Labor"** – Dr. Julian T. Parer
11:30–12:30 **"Dysfunctional Labor"** – Dr. Schifrin

Sunday, July 18, 1993
7:00 a.m. **Registration & Breakfast**
7:30–8:30 **"Intrapartum Fetal Monitoring"** – Dr. Parer
8:30–9:30 **"Ketoacidosis"** - Dr. Benedetti
9:30–10:30 **"Pre-Eclampsia Including HELLP Syndrome"** – Dr. Parer
10:30–11:30 **"Invasive Hemodynamic Monitoring"** - Dr. Benedetti
11:30–12:30 **"Will the C/Section Rate Ever Exceed 100%?"** – Dr. Schifrin

"The GYN CME Fund designates these continuing medical education activities for 10 credit hours each in Category 1 of the Physician's Recognition Award of the American Medical Association."

"The GYN CME Fund is accredited by the Nevada State Medical Association to sponsor continuing medical education for physicians."

"The American College of Obstetricians and Gynecologists has assigned ten cognates each (Formal Learning) to these programs."

"These programs have been reviewed and are acceptable for ten elective hours each by the American Academy of Family Physicians."

"Application for nursing CE approval has been made to University Medical Center Department of Staff Development."

For Seminar Information Write or Call:

GYN CME FUND, INC.
2570 S. Bruce Street, Ste. B–4
Las Vegas, Nevada 89109
1-800-683-OBGY (6249)
In Las Vegas 1-702-732-0710

For Hotel Reservations Call: 1-800-634-3101

(Continued from Page 476)

October 23-24—**Fifteenth Annual Perinatal Conference.** Children's Hospital of Denver in Fort Collins. Fri-Sat. Contact: Sharon Adams, (303) 861-6946 or (800) 225-0010.

November 9-13—**38th Annual Family Practice Review.** University of Colorado Health Sciences Center, Denver. Wed-Sun. Contact: U of Colo.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

January 11-15—**Twenty-Fourth Annual Cardiovascular Conference at Snowmass.** American College of Cardiology at the Convention Center, Snowmass Resort, Snowmass. Mon-Fri. Contact: Margaret Sgro, American College of Cardiology, (800) 257-4739.

January 22-24—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs Medical Center at Beaver Run Resort and Conference Center, Breckenridge. Fri-Sun. Contact: Victoria Hall or Karen Babcock, (303) 393-2826, or FAX (303) 393-4656.

January 23-30—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Tamarron Resort, Durango. Sat-Sat. Contact: U of Colo.

February 22-26—**Colorado Conference on Contemporary Family Practice.** University of Colorado School of Medicine at Breckenridge. Mon-Fri. Contact: U of Colo.

February 27-March 5—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Vail. Sat-Fri. Contact: U of Colo.

February 27-March 6—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Sat. Contact U of Colo.

February 28-March 5—**ENT Ski Conference.** University of Nebraska Medical Center Continuing Medical Education Program at Keystone Resort, Keystone. Sun-Fri. Contact: Brenda C. Ram, University of Nebraska Continuing Education, (402) 559-4152.

March DTBA—**Fifth Annual Colorado Geriatrics Overview.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. Contact: U of Colo.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195 or (800) 882-9153, FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 22-24—**Practical Orthopaedics in the Primary Care Setting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 22-24—**Infectious Disease: Issues and Challenges in Obstetrics and Gynecology.** Hyatt Regency, Albuquerque. Thurs-Sat. Contact: UNM SOM.

October 30-November 1—**The Emotional Life of the Infant: Clinical Applications.** Hilton Hotel, Albuquerque. Fri-Sun. Contact: UNM SOM.

November 6—**Controversies in the Care of the Dying Patient.** Albuquerque. Fri. Contact: Mary R. Boning, Presbyterian Healthcare Services, PO Box 26666, Albuquerque 87125. (505) 841-1225.

November 6-7—**4th Annual New Mexico Parent/Professional Education Conference on Childhood Cancer.** Albuquerque. Fri-Sat. Contact: UNM SOM.

November 6-7—**Update for Radiographers.** Four Seasons Quality Inn, Albuquerque. Fri-Sat. Contact: UNM SOM.

December 3-5—**American College of Physicians, New Mexico Chapter, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM.

December 11-12—**Trauma Update 1992.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

SPONSORS OF COURSES—ABBREVIATIONS

CH	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501 (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

(Continued on Page 479)

INTERNISTS

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CONTINUING MEDICAL EDUCATION

(Continued from Page 478)

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

October 20-23—**Development and Application of Biomarkers to the Study of Human Health Ethics.** Seattle. Tues-Fri. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.

October 22—**Pain Management.** Everett. Thurs. Contact: PNMEI, (206) 258-6322.

October 23—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

October 23—**NPCCare Consortium.** Seattle. Fri. Contact: Children's Hospital, (206) 526-2501.

October 30—**Perinatology.** Fri. Tacoma. Contact: Multicare, (206) 594-1221.

October 30—**Preventative Health Care in the Elderly.** Seattle. Fri. Contact: Northwest Hospital, (206) 368-1623.

October 30-31—**Primary Care for Women.** Seattle. Fri-Sat. Contact: VMMC.

October 30-31—**Black Culture Health.** Seattle. Fri-Sat. Contact: Providence Hospital, (206) 320-2552.

October 31-November 1—**PALS Instructor Course.** Seattle. Sat-Sun. Contact: Children's Hospital, (206) 526-2501.

November 6—**Infectious Disease Update.** Tacoma. Fri. Contact: PCMS CME.

November 12—**Dermatology.** Thurs. Everett. Contact: PNMEI, (206) 258-6322.

November 12-13—**Advances in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 14-15—**Travel Medicine Update.** Seattle. Sat-Sun. Contact: U/W.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

November 20—**GI Day.** Seattle. Fri. Contact: PCMS CME.

November 21—**Arthrocentesis & Injection Techniques.** Seattle. Sat. Contact: U/W.

December 4—**Rehabilitation Issues in Aging.** Seattle. Fri. Contact: U/W.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-11—**ACLS Course.** Tacoma. Thurs. Contact: PCMS CME.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

December 10-12—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 15-16—**Introduction to Industrial Hygiene.** Seattle. Tues-Wed. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898. ◆

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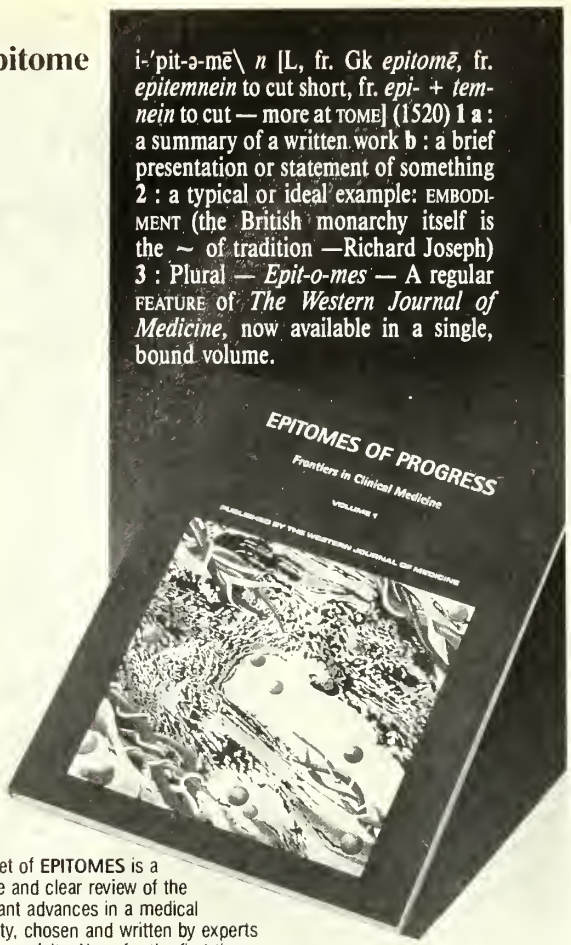

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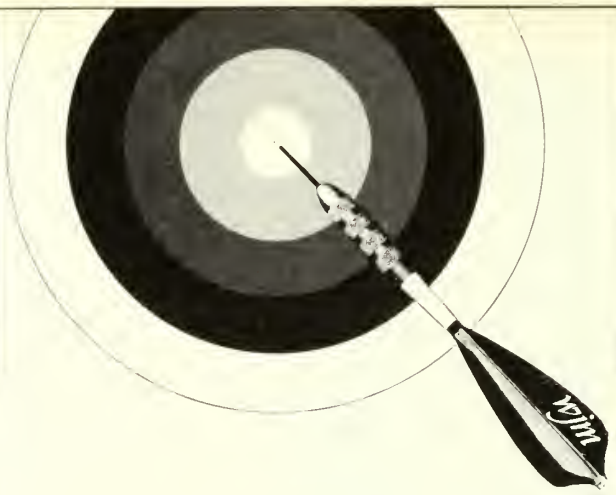

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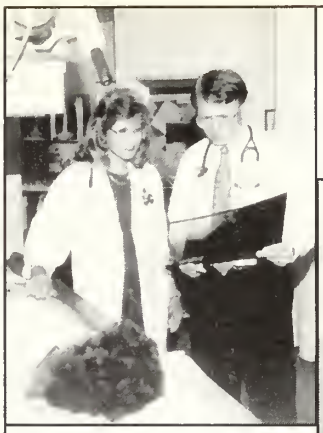

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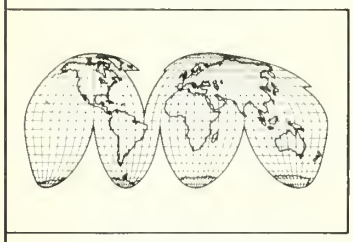

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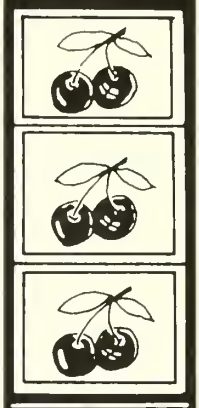

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ESCAPE those urban hassles and come to scenic northern California, southern California, and Phoenix, Arizona. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Mark Oswald of Gielow/Laske Associates, Inc, 306 N Milwaukee St, Milwaukee, WI 53202; (800) 969-7715, FAX (414) 226-4131. Confidential inquiries welcome.

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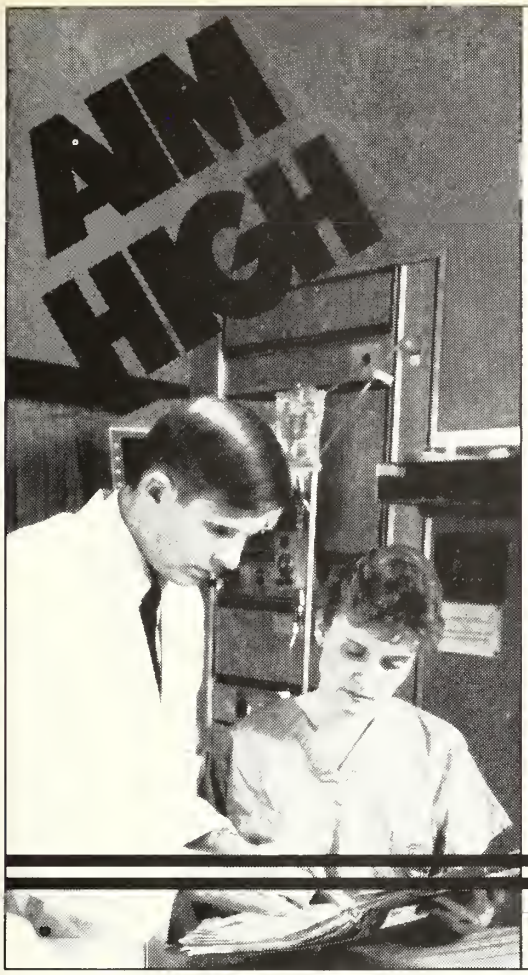

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OB/GYN – Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BC/BE OB/GYN AND FAMILY PRACTITIONER with commitment to caring for the underserved, needed to join one Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs and four Family Physicians. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, NHSC loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

INTERNIST BC/BE to join 10 physician (OB, Pediatrics, Internal Medicine), Primary Care community health clinic in Toppenish, Washington serving migrant and seasonal farm workers with common as well as Third World maladies. Reasonable call schedule with 3.5 Internal Medicine department. Rural setting, beautiful, sunny central Washington near Columbia River Gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and professional liability. Contact Ann Garza, Director of Personnel, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

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Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1993, Loew's Ventana, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1993, date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1993, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-15, 1993, Society Office, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): November 6-8, 1992, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1993, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 19-21, 1993, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

AUDIO-DIGEST FOUNDATION 411

BLUE CROSS OF CALIFORNIA
California Care 396, 397

BRISTOL-MEYERS SQUIBB COMPANY
Provochol 399, 400, 401, 402

BROWNING-FERRIS INDUSTRIES
Medical Waste Systems 395

CIGNA HEALTHPLAN 483, 485

CLASSIFIED ADVERTISING 481, 482, 483, 484, 485, 486, 487, 488, 489, 490

CNA ..... 3rd Cover

COMPHEALTH 490

DOMUS MEDICAL MANAGEMENT 407

ELI LILLY & COMPANY
Humulin 409

450 SUTTER MEDICAL/DENTAL BUILDING
San Francisco 479

GYN CME FUND 477

HOFFMANN LA ROCHE INC.
Valium ..... 4th Cover

KAISER PERMANENTE 489

MARION MERRELL DOW
Cardizem 415, 416

ORLANDO REGIONAL MEDICAL CENTER 417

PALISADES PHARMACEUTICALS INC.
Yacan 407

SANDOZ PHARMACEUTICALS
DynaCirc ..... 2nd Cover, 391, 392

G.D. SEARLE & COMPANY
Calan SR 405

SMITHKLINE BEECHAM PHARMACEUTICALS
Tagamet 419, 420

SOUTHWEST MEDICAL ASSOCIATES 483

SUTTER NEUROSCIENCE CENTER 475

UNIVERSITY OF SOUTHERN CALIFORNIA
University Hospital 412, 413

US AIR FORCE 487

US ARMY 486

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Epitomes of Pragress 480
Special Issues 393
Subscription 480

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The Western Journal of Medicine

VOLUME 157 • NUMBER 5 NOVEMBER 1992

ARTICLES

527 Abdominal Aortic Aneurysm—Incidence in a Hospital Population at Risk
H M LAZARUS

530 Radiation Retinopathy
R W ZAMBER and J L KINYOUN

534 Effects of the Multiple Risk Factor Intervention Trial Smoking Cessation Program on Pulmonary Function—A Randomized Controlled Trial
W S BROWNER, A G DU CHENE, and S B HULLEY

539 Medications in Older Patients
M HOBSON

NFERENCES AND REVIEWS

e Up and Smell the Coffee—Caffeine, Coffee, and the ical Consequences
issant: T CHOU

ary Tract Infections in Children—An Update
IKOVIC, R D ADELMAN, and P A NANCARROW

TOMES

ortant Advances in Anesthesiology

ERTS, NOTICES, AND CASE REPORTS

ultaneous Reconstruction of the Abdominal Aorta and ecystectomy—A Peer Review Perspective
HEYDORN and W H MONCRIEF, Jr

ise Demyelinating Lesions of the Brain After the Rapid elopment of Hypernatremia
CLARK

Adult Still's Disease Presenting as Fever of Undetermined Origin in a Patient With Leukemoid Reaction
B A MIZOCK and G BALAMUNISWAMY

SPECIAL SERIES

576 Costs and Coverage—Pressures Toward Health Care Reform
P R LEE, D SOFFEL, and H S LUFT

EDITORIALS

584 Health Care Reform—Another View • Getting Some Breathing Room—Persuading Patients to Stop Smoking • Caffeine Under Examination—A Passing Grade • Urinary Tract Infections—Navigating Complex Currents • Osmotic Shifts, Metabolic Compromise, and the Vulnerability of the Pons

CORRESPONDENCE

591 Earthquakes and the Practicing Physician • Blood-Saturated Shoe Covers • Put Your Money Where Your Advice Is • Let's Not Do With Euthanasia What We Did With Abortion

OTHER FEATURES

493 Subscription Information

511 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington

516 In Memoriam

533 Poem

594 Instructions for Authors

596 Classified Advertising

606 Western State Medical Associations' Meetings

Detailed Table of Contents: 502, 504, 508

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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Please see adjacent page
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Rogaine® Rx

TOPICAL SOLUTION minoxidil 2%

INDICATIONS AND USAGE
ROGAINE is indicated for treatment of androgenetic alopecia, expressed in men as male pattern baldness of the vertex and in females as diffuse hair loss or thinning of the frontoparietal areas. At least 4 months of twice daily applications are necessary before evidence of hair growth can be expected

CONTRAINDICATIONS
Hypersensitivity to minoxidil, propylene glycol, or ethanol.

WARNINGS
1 Need for normal scalp. Before starting treatment, make sure that the patient has a normal, healthy scalp Local abrasion or dermatitis may increase absorption and hence the risk of side effects.
2 Potential adverse effects. Although extensive use of topical minoxidil has not revealed evidence that enough minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, or unusual sensitivity could, at least theoretically, produce a systemic effect
Experience with oral minoxidil has shown the following major cardiovascular effects (Review the package insert for LONITEN* Tablets for details):
– salt and water retention, generalized and local edema
– pericardial effusion, pericarditis, tamponade
– tachycardia
– increased incidence of angina or new onset of angina
Patients with underlying heart disease, including coronary artery disease and congestive heart failure, would be at particular risk of these potential effects Additive effects could also emerge in patients being treated for hypertension
Potential patients should have a history and physical and should be advised of potential risks A risk/benefit decision should be made. Heart patients should realize that adverse effects may be especially serious.
Alert patients to the possibility of tachycardia and fluid retention and monitor for increased heart rate, weight gain, or other systemic effects.

PRECAUTIONS
General Precautions. Monitor patients 1 month after starting ROGAINE and at least every 6 months thereafter Discontinue ROGAINE if systemic effects occur
The alcohol base will burn and irritate the eye If ROGAINE reaches sensitive surfaces (eg, eyes, abraded skin, and mucous membranes), bathe with copious cool water
Avoid inhaling the spray.
Do not use in conjunction with other topical agents, such as corticosteroids, retinoids and petrolatum, or agents that enhance percutaneous absorption.
ROGAINE is for topical use only Each mL contains 20 mg minoxidil, and accidental ingestion could cause adverse systemic effects
Decreased integrity of the epidermal barrier caused by inflammation or disease of the skin, eg, excoriations, psoriasis, or severe sunburn, may increase minoxidil absorption
Patient Information A patient information leaflet is included with each package and in the full product information
Drug Interactions No drug interactions are known. Theoretically, absorbed minoxidil may potentiate orthostatic hypotension in patients taking guanethidine
Carcinogenesis, Mutagenesis, and Impairment of Fertility No carcinogenicity was found with topical application Oral administration may be associated with an increased incidence of malignant lymphomas in female mice and hepatic nodules in male mice In rats, there was a dose-dependent reduction in conception rate.
Pregnancy Category C. ROGAINE should not be used by pregnant women
Labor and Delivery The effects are not known
Nursing Mothers ROGAINE should not be administered to nursing mothers
Pediatric Use: Safety and effectiveness has not been established for patients under age 18
Postmenopausal Use Efficacy in postmenopausal women has not been studied

ADVERSE REACTIONS
ROGAINE was used by 3,857 patients (347 females) in placebo-controlled trials Except for dermatologic events, no individual reaction or reactions grouped by body systems appeared to be increased in the minoxidil-treated patients
Dermatologic: irritant or allergic contact dermatitis – 7 36%, **Respiratory:** bronchitis, upper respiratory infection, sinusitis – 7 16%, **Gastrointestinal:** diarrhea, nausea, vomiting – 4 33%, **Neurologic:** headache, dizziness, faintness, light-headedness – 3 42%, **Musculoskeletal:** fractures, back pain, tendinitis – 2 59%, **Cardiovascular:** edema, chest pain, blood pressure increases/decreases, palpitations, pulse rate increases/decreases – 1.53%, **Allergic:** nonspecific allergic reactions, hives, allergic rhinitis, facial swelling, sensitivity – 1 27%, **Metabolic-Nutritional:** edema, weight gain – 1 24%, **Special Senses:** conjunctivitis, ear infections, vertigo – 1 17%, **Genital Tract:** prostatitis, epididymitis, vaginitis, vulvitis, vaginal discharge/itching – 0 91%, **Urinary Tract:** urinary tract infections, renal calculi, urethritis – 0 93%, **Endocrine:** 0 47%; **Psychiatric:** anxiety, depression, fatigue – 0.36%, **Hematologic:** lymphadenopathy, thrombocytopenia – 0 31%
Patients have been followed for up to 5 years, and there has been no change in incidence or severity of reported reactions Additional events have been reported since marketing and include eczema, hypertrichosis, local erythema, pruritus, dry skin/scalp flaking, sexual dysfunction, visual disturbances, including decreased visual acuity, exacerbation of hair loss; and alopecia

DOSAGE AND ADMINISTRATION
Hair and scalp should be dry before application 1 mL should be applied to the total affected areas twice daily Total daily dose should not exceed 2 mL If the fingertips are used to facilitate drug application, wash the hands afterwards. If hair regrowth is realized, maintenance of twice daily applications is necessary for additional and continued hair regrowth

HOW SUPPLIED
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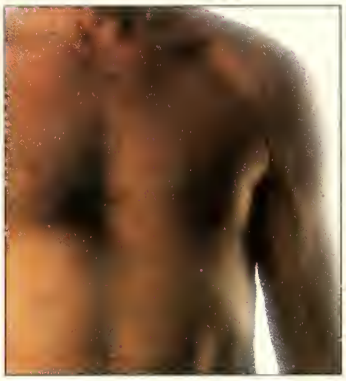

Maintains cardiac performance.

- No significant effect on heart rate*[7-10]
- No adverse effect on cardiac conduction[11,12] or contractility†[3,10,13-15]
- No alteration of digoxin clearance[16]

Does not compromise metabolic parameters.

- No clinically significant effect on serum glucose metabolism[17]
- No effect on glucose tolerance, insulin secretion or insulin action in NIDDM patients[17]
- No clinically significant effect on lipid metabolism[18,19]

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- No known contraindications except for hypersensitivity to DynaCirc
- No significant interactions with the 20 most-commonly prescribed drugs‡
- Effectively reduces diastolic and systolic blood pressure without orthostatic hypotension§[7,20,21]
- Side effects are usually minimal and transient¶[7,20-23]
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  - —Rare incidence of constipation or cough (<1%)
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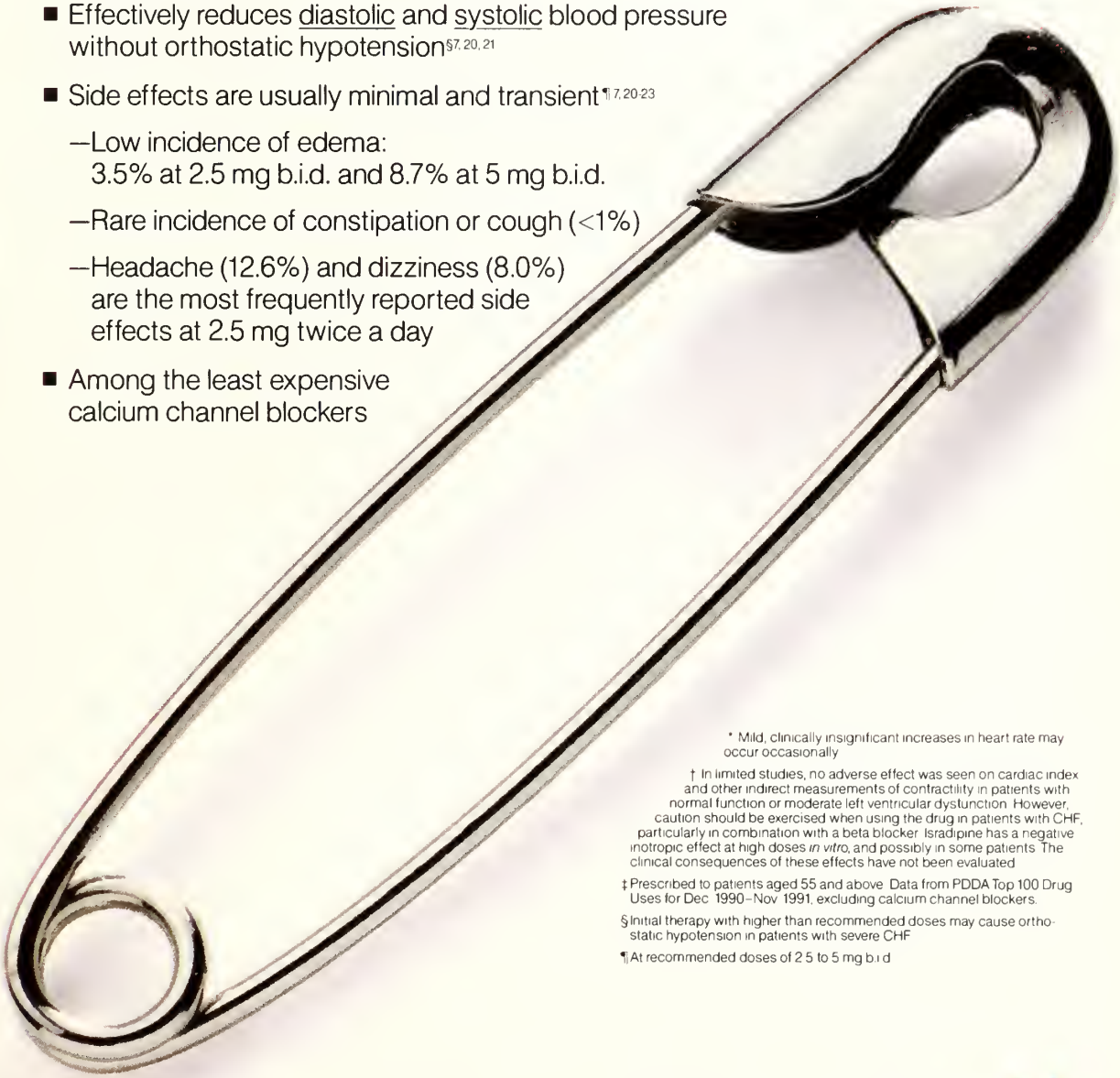

* Mild, clinically insignificant increases in heart rate may occur occasionally

† In limited studies, no adverse effect was seen on cardiac index and other indirect measurements of contractility in patients with normal function or moderate left ventricular dysfunction. However, caution should be exercised when using the drug in patients with CHF, particularly in combination with a beta blocker. Isradipine has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. The clinical consequences of these effects have not been evaluated.

‡ Prescribed to patients aged 55 and above. Data from PDDA Top 100 Drug Uses for Dec. 1990–Nov. 1991, excluding calcium channel blockers.

§ Initial therapy with higher than recommended doses may cause orthostatic hypotension in patients with severe CHF.

¶ At recommended doses of 2.5 to 5 mg b.i.d.

DynaCirc®

2.5 mg capsules (isradipine) 5 mg capsules

For Safety's Sake™

Please see following page for brief summary of full Prescribing Information.

BRIEF SUMMARY
Please see package insert for full prescribing information.

DYNACIRC® (isradipine) CAPSULES

INDICATION

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None.

PRECAUTIONS

General: *Blood Pressure*. Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses. *Use in Patients with Congestive Heart Failure*. Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker. **Drug Interactions**: *Nitroglycerin*. DynaCirc® has been safely coadministered with nitroglycerin. *Hydrochlorothiazide*. A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect. *Propranolol*: In a single dose study in normal volunteers coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol. *Digoxin*. The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, nonrenal and total body clearance of digoxin. *Fentanyl Anesthesia*: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. A comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats. **Pregnancy**: *Pregnancy Category C*: There are no adequate and well controlled studies in pregnant women. DynaCirc® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers**: It is not known whether DynaCirc® is excreted in human milk. A decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**: Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience. Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia), and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions (vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations, and gastrointestinal disturbances. The following adverse reactions have been reported by 1% or greater of patients receiving DynaCirc® at any dose (N=934): headache (13.7%), dizziness (7.3%), edema (7.2%), palpitations (4.0%), fatigue (3.9%), flushing (2.6%), chest pain (2.4%), nausea (1.8%), dyspnea (1.8%), abdominal discomfort (1.7%), tachycardia (1.5%), rash (1.5%), pollakiuria (1.5%), weakness (1.2%), vomiting (1.1%), diarrhea (1.1%). The following adverse events were reported in 0.5-1% of the isradipine-treated patients in hypertension studies, or are rare, but more serious events from this and other data sources, including postmarketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain. **Skin**: pruritus, *urticaria*. **Musculoskeletal**: cramps of legs/feet. **Respiratory**: cough. **Cardiovascular**: shortness of breath, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure*. **Gastrointestinal**: abdominal discomfort, constipation, diarrhea. **Urogenital**: nocturia. **Nervous System**: drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, *syncope, paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke*. **Autonomic**: hyperhidrosis, visual disturbance, dry mouth, numbness. **Miscellaneous**: throat discomfort, *leukopenia, elevated liver function tests*.

[DECEMBER 31, 1990 DYN-Z2]

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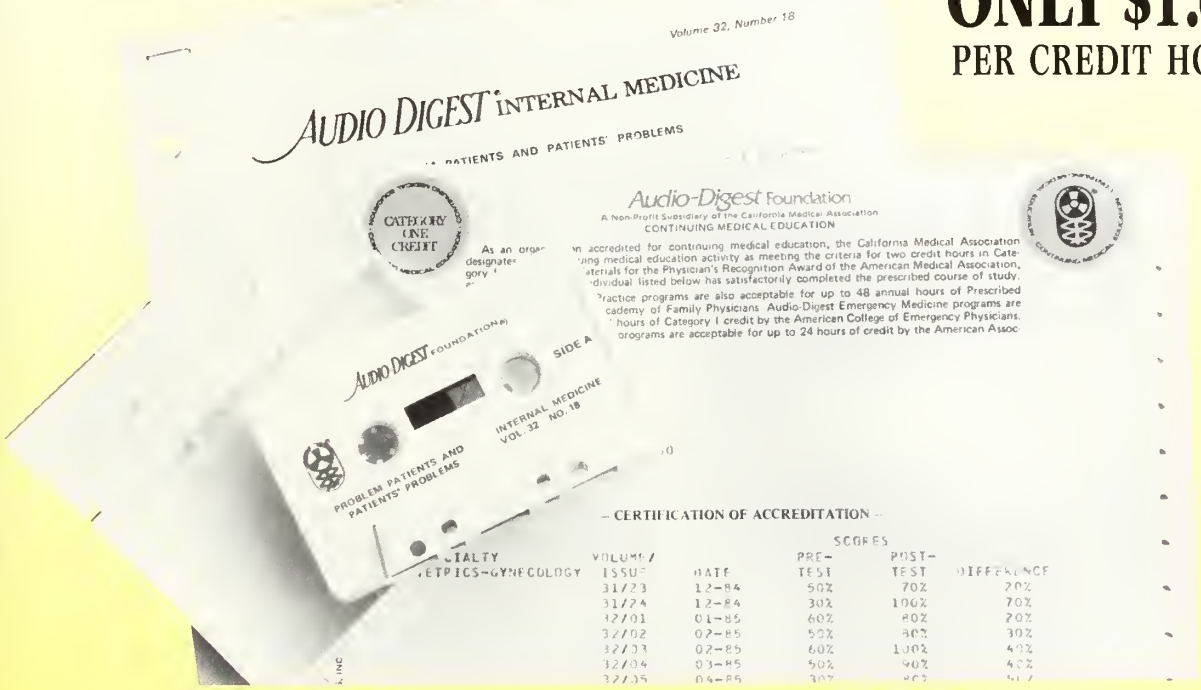

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To determine whether the decline in pulmonary function in smokers is modified by stop-smoking intervention, a randomized controlled study (the Multiple Risk Factor Intervention Trial) was done comparing participants in a special intervention group that included an intensive smoking cessation program with those assigned to usual care. The subjects were 6,347 middle-aged male smokers who had serial measurements of pulmonary function—principally the forced expiratory volume in 1 second (FEV_1)—during 6 to 7 years of follow-up. No overall differences were detected in the rate of loss of FEV_1 in the two groups. The use of β-blockers, which had detrimental effects on FEV_1, was significantly more common in the intervention group. Among nonusers of β-blockers, heavy smokers lost FEV_1 at a rate about 11 ml per year slower in the intervention group than in the control group ($2P = .09$) and ended the trial with an FEV_1 about 90 ml higher ($2P = .05$). These results support the inference from observational studies that smoking cessation has a beneficial effect on pulmonary function in heavy smokers.

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VOLUME 157 • NUMBER 5 • NOVEMBER 1992

CONTENTS

ARTICLES

527 **Abdominal Aortic Aneurysm—Incidence in a Hospital Population at Risk**

HARRISON M. LAZARUS, MD

From FHP Health Care, LDS Hospital and University of Utah School of Medicine, Salt Lake City.

530 **Radiation Retinopathy**

RONALD W. ZAMBER, MD, and JAMES L. KINYOUN, MD

From the Department of Ophthalmology, University of Washington School of Medicine, Seattle.

534 **Effects of the Multiple Risk Factor Intervention Trial Smoking Cessation Program on Pulmonary Function—A Randomized Controlled Trial**

WARREN S. BROWNER, MD, MPH; ALAIN G. DU CHENE; and STEPHEN B. HULLEY, MD, MPH

From the Division of Clinical Epidemiology, Department of Epidemiology and Biostatistics, University of California, San Francisco, School of Medicine; the General Internal Medicine Section, Department of Medicine, Veterans Affairs Medical Center, San Francisco; and the Multiple Risk Factor Intervention Trial Coordinating Center, Minneapolis, Minnesota.

539 **Medications in Older Patients**

MANA HOBSON, MD

From the Department of Medicine, Division of General Internal Medicine, University of California, San Francisco, School of Medicine, and the Hospital Based Home Care, Division of General Internal Medicine, Veterans Affairs Medical Center, San Francisco, California.

CONFERENCES AND REVIEWS

544 **Wake Up and Smell the Coffee—Caffeine, Coffee, and the Medical Consequences**

Discussant: TONY CHOU, MD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

554 **Urinary Tract Infections in Children—An Update**

ISRAEL ZELIKOVIC, MD; RAYMOND D. ADELMAN, MD; and PAUL A. NANCARROW, MD

From the Division of Nephrology, Department of Pediatrics, University of Washington School of Medicine, Seattle; the Department of Pediatrics, Eastern Virginia Medical School, Norfolk; and the Department of Radiology, Children's Hospital of Northern California, Oakland.

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562 **Transesophageal Echocardiography**

TIMOTHY L. FENG and DANIEL G. BLANCHARD, MD

563 **New Applications of Propofol**

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(Continued on Page 504)

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†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil In Focus.* New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol.* 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow release verapamil in essential hypertension. *Eur J Clin Pharmacol.* 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation.* 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology.* 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

2/13/92 • P92CA7196V

Address medical inquiries to:
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(Continued from Page 502)

563 'Do-Not-Resuscitate' Orders in Operating Rooms
WENDELL C. STEVENS, MD

564 Novel Approaches to the Treatment of Neuropathic Pain
ROBERT W. PRESLEY, MD

564 Postoperative Pain
KENNETH DRASNER, MD

565 Perioperative Myocardial Ischemia
JACQUELINE M. LEUNG, MD

566 Sedating Patients in Intensive Care Units
MAGED S. MIKHAIL, MD, and DURAIYAH THANGATHURAI, MD

566 Perioperative Temperature Control
DANIEL I. SESSLER, MD

567 Postoperative Apnea Syndrome in Premature Infants
DAVID J. STEWARD, MD

567 Autologous Blood Transfusion Therapy
STEPHEN H. JACKSON, MD

ALERTS, NOTICES, AND CASE REPORTS

569 Simultaneous Reconstruction of the Abdominal Aorta and Cholecystectomy—A Peer Review Perspective
WILLIAM H. HEYDORN, MD, and WILLIAM H. MONCRIEF, Jr, MD
From the Departments of Surgery, University of California, San Francisco, School of Medicine, and Uniformed Services University of the Health Sciences, Bethesda, Maryland; and California Medical Review, Inc, San Francisco.

571 Diffuse Demyelinating Lesions of the Brain After the Rapid Development of Hypernatremia
WILLIAM R. CLARK, MD
From the Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis.

573 Adult Still's Disease Presenting as Fever of Undetermined Origin in a Patient With Leukemoid Reaction
BARRY A. MIZOCK, MD, and GEETHA BALAMUNISWAMY, MD
From the Medical Intensive Care Unit and the Department of Medicine, Cook County Hospital, Chicago, Illinois.

SPECIAL SERIES

576 Costs and Coverage—Pressures Toward Health Care Reform
PHILIP R. LEE, MD; DENISE SOFFEL, PhD; and HAROLD S. LUFT, PhD
From the Institute for Health Policy Studies, University of California, San Francisco, School of Medicine.

EDITORIALS

584 Health Care Reform—Another View

585 Getting Some Breathing Room—Persuading Patients to Stop Smoking
FRANK E. SPEIZER, MD
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(Continued on Page 508)

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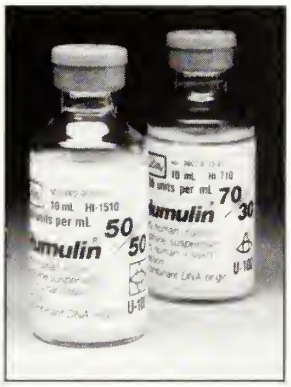

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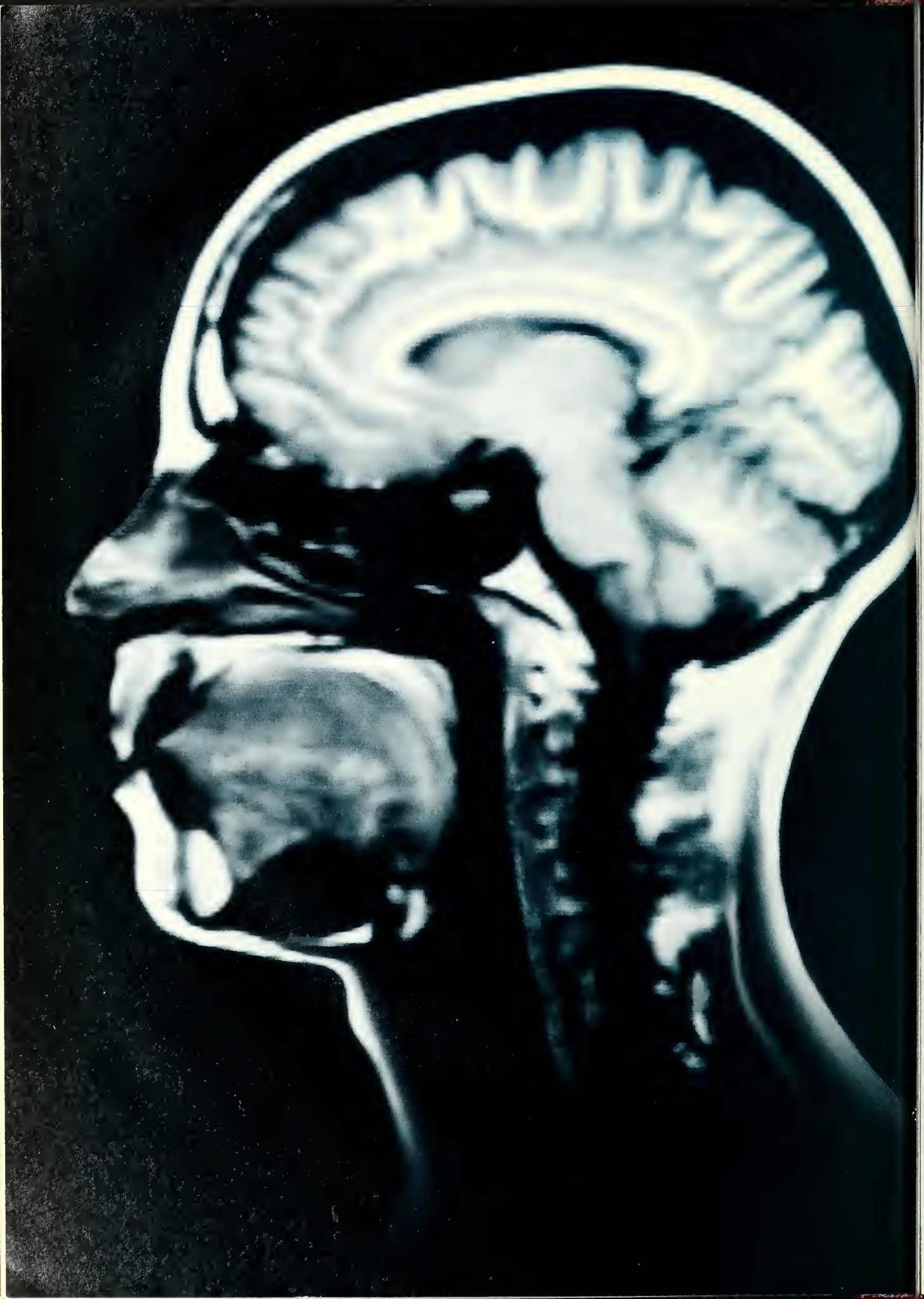

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(Continued from Page 504)

586 Caffeine Under Examination—A Passing Grade
MARTIN G. MYERS, MD, FRCPC
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587 Urinary Tract Infections—Navigating Complex Currents
MARY ANN CARMACK, PhD, MD, and ANN M. ARVIN, MD
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588 Osmotic Shifts, Metabolic Compromise, and the Vulnerability of the Pons
ANN C. McKEE, MD
Dr McKee is Assistant Professor, Charles S. Kubick Laboratory of Neuropathology, Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston.

CORRESPONDENCE

591 Earthquakes and the Practicing Physician
CARL H. SCHULTZ, MD, and KRISTI L. KOENIG, MD

591 Blood-Saturated Shoe Covers
PEDRO A. RUBIO, MD

592 Put Your Money Where Your Advice Is
JOSEPH A. ABBOTT, MD

592 Let's Not Do With Euthanasia What We Did With Abortion
GEORGE B. MARKLE IV, MD

OTHER FEATURES

493 Subscription Information

511 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; New Mexico; Utah; Washington

516 In Memoriam

533 Poem

594 Instructions for Authors

596 Classified Advertising

606 Western State Medical Associations' Meetings

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450; the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system, these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIAL

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9
Dizziness	22 (7%)	6 (2.8
Edema	19 (6%)	2 (0.9
Bradycardia	19 (6%)	3 (1.4
ECG Abnormality	13 (4.1%)	3 (1.4
Asthenia	10 (3.2%)	1 (0.5
Constipation	5 (1.6%)	2 (0.9
Dyspepsia	4 (1.3%)	1 (0.5
Nausea	4 (1.3%)	2 (0.9
Palpitations	4 (1.3%)	2 (0.9
Polyuria	4 (1.3%)	2 (0.9
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5
Hypotension	3 (1%)	1 (0.5
Insomnia	3 (1%)	1 (0.5
Rash	3 (1%)	1 (0.5
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions rep placebo-controlled trials in patients receiving CARDIZEM CD up to 360 rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARD Capsules involving over 3000 patients, the most common events (ie, than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than

Cardiovascular: Angina, arrhythmia, AV block (second- or third-d bundle branch block, congestive heart failure, ECG abnorm hypotension, palpitations, syncope, tachycardia, ven extrasystoles

Nervous System: Abnormal dreams, amnesia, depression, gait abno hallucinations, insomnia, nervousness, paresthesia, personality somnolence, tinnitus, tremor

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeu elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irr hyperglycemia, hyperuricemia, impotence, muscle cramp congestion, nocturia, osteoarticular pain, polyuria, sexual diffic

The following postmarketing events have been reported infrequ patients receiving CARDIZEM: alopecia, erythema multiforme, ex dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic increased bleeding time, leukopenia, purpura, retinopath thrombocytopenia. In addition, events such as myocardial infarct been observed which are not readily distinguishable from the nature of the disease in these patients. A number of well-documented generalized rash, characterized as leukocytoclastic vasculitis, hav reported. However, a definitive cause and effect relationship betwe events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages c

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of

CARDIZEM® CD Product Information as of October 1991

CARDIZEM® SR Product Information as of January 1991

References: 1. Data on file, Marion Merrell Dow Inc. 2. Cramer JA, Me Prevey ML, et al. JAMA 1989;261(22):3273-3274

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ANESTHESIOLOGY

November 20-21—**Pain Management Conference.** UCD at Silverado Country Club. Fri-Sat. 12 hrs. $225. Contact: UCD.

January 6-9—**Anesthesia Update.** UCSD at Hotel del Coronado. Wed-Sat. Contact: UCSD.

January 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach, Maui, Hawaii. 1 wk. 21 hrs. $395. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

January 29-31—**31st Clinical Conference in Pediatric Anesthesiology.** Children's Hospitals Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Erancisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD. University of California, Davis
Contact: Ruth Eeryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

March 19-23—**67th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Diego Marriott Hotel & Marina, San Diego. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131-2553. (216) 642-1124.

March 26-28—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort, Dana Point. Fri-Sun. 9 hrs. $175-$245. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

CARDIOLOGY

December 11-13—**Tenth Anniversary: Advances in Heart Disease.** American College of Cardiology at Grand Hyatt Hotel, San Francisco. Fri-Sun. 17 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

January 21-23—**Cardiology '93.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, Conference Manager, PO Box 2586, La Jolla 92038. (619) 459-1564.

March 11-13—**3rd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 26-28—**Thromboembolic & Primary Vascular Disease: Diagnosis & Management.** UCSD at Sheraton Harbor Island. Fri-Sun. Contact: UCSD.

DERMATOLOGY

January 15-17—**Practical Dermatology & Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. Contact: UCSD.

January 22-24—**Cutaneous Malignancies: 1993 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. $350. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

November 21-22—**Advanced Cardiac Life Support Provider Course.** Life Support Associates at Holy Cross Medical Center. Sat-Sun. Contact: Steve Rodgers, Life Support Associates, 2525 Briarglen Rd, Acton 93510-2109. (800) 310-2257.

December 5-6—**Advanced Cardiac Life Support Provider Course.** Life Support Associates at Orthopaedic Hospital. Sat-Sun. Contact: Steve Rodgers, Life Support Associates, 2525 Briarglen Rd, Acton 93510-2109. (800) 310-2257, ext. 71.

December 6-11—**Current Concepts in Emergency Care: 13th Annual Conference.** American College of Emergency Physicians Washington Chapter at Maui Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. Contact: Jeannine Whidbee, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 7-11—**Emergency Medicine Symposia II.** UCSD at La Jolla Marriott. Mon-Fri. Contact: UCSD.

January 13-17—**The California Trauma Conference.** UCSD at Hotel del Coronado. Mon-Fri. 20 hrs. $400. Contact: UCSD.

January 18-22—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

January 23-30—**Wound Management.** UCSD at Royal Waikoloan, Kohala Coast, Island of Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-27—**Update: Controversies in Emergency & Primary Care.** American Institute of Postgraduate Education at Royal Lahaina Resort, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 21-26—**Emergency Medicine: 1993.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

March 15-19—**Emergency Medicine Symposia II.** UCSD at La Jolla. Mon-Fri. Contact: UCSD.

March 31-April 3—**Advances in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Wed-Sat. 19 hrs. Contact: UCSF.

(Continued on Page 520)

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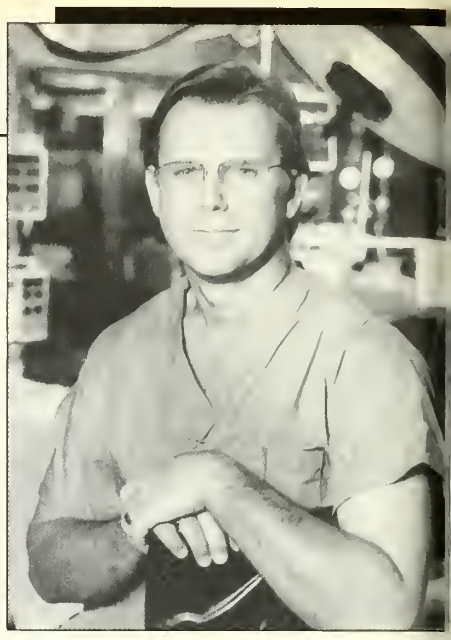

Vaughn A. Starnes, M.D. has joined the University of Southern California School of Medicine.

Vaughn A. Starnes, M.D., has joined the University Southern California School of Medicine as Professor Surgery, Chief of the Division of Cardiothoracic Surge and Director of the USC Cardiothoracic Center at US University Hospital, Childrens Hospital Los Angeles and L Angeles County+USC Medical Center. Dr. Starnes is a worl recognized leader and innovator in adult and pediatric hea heart-lung and lung transplantation and treatment of congenit heart disease.

In 1984 Dr. Starnes was accepted to the Stanford Cardiothor cic program, where he completed two years as a resident in cardi vascular surgery, and one year as chief resident in cardio transplantation under the guidance of Norman Shumway, M.D.

In 1988 Dr. Starnes was appointed director of Stanford's hea lung transplantation program, and later became chief of pediat heart surgery and director of the transplant program at Stanfor Lucile Salter Packard Childrens Hospital. He performed about 40 adult and pediatric cardiac cases annually at Stanford. In additi to his adult cardiothoracic surgical expertise, Dr. Starnes earned national reputation for his work in pediatrics.

Dr. Starnes also pioneered lung and heart-lung transplant pr cedures in children that previously had only been performed c adults. In 1991 he was the first surgeon to transplant the le upper lobe of a 2-year-old donor into a newborn with pulmona hypertension who could not be weaned off ECMO (Extracorpore Membrane Oxygenation). In 1992, he performed the first lu transplant on a baby with congenital diaphragmatic hernia.

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e arrival of Vaughn A. Starnes, M.D., the University of Southern California hool of Medicine marks a new era of cellence in the treatment of cardiovas- lar disease. This commitment is exem- fied in the creation of the USC rdiothoracic Center at USC University spital, Childrens Hospital Los Angeles d Los Angeles County+USC Medical nter.

mprehensive Services

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The Center features a non-invasive vas- lar diagnostic laboratory, diagnostic giography laboratory and state-of-the- cardiac catheterization laboratories. If licated, cardiac surgeons incorporate latest corrective surgical techniques conditions such as ventricular and ial arrhythmias and aortic diseases that olve aneurysms and dissections.

The Center also specializes in the treat- nt of infants with congenital heart fects including hypoplastic left heart drome, aortic valve disease, and trans- sition of the great vessels.

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At the Center, cardiologists, cardiothoracic surgeons, vascular surgeons, anesthesiologists, radiologists, interventional radiologists and allied medical professionals pool their extensive knowledge and expertise to provide patients with the full range of diagnostic and treatment alternatives.

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As a university-based program, the Center is actively engaged in research. Specialists identify clinical problems and then seek the answer in the laboratory. Patients benefit from this link between bench and bedside, which promises to provide a better understanding of the physiology of the disease process.

Community Resource

As a vital component of the USC School of Medicine, the USC Cardiothoracic Center serves as a key educational resource for community-based and referring physicians. Physicians are encouraged to contact the Center through PACE to obtain telephone consultations, and access information regarding new patient care techniques, medications and research protocols to receive assistance with patient management concerns.

A new era is unfolding at the USC School of Medicine. We invite you to be a part of it. For more information about the USC Cardiothoracic Center, or to refer a patient, dial:
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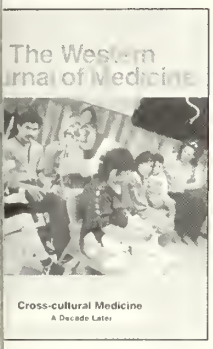

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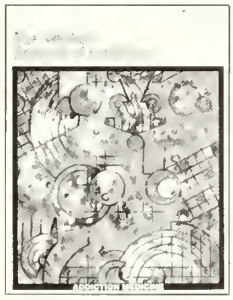

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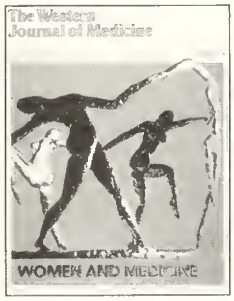

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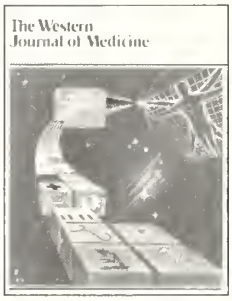

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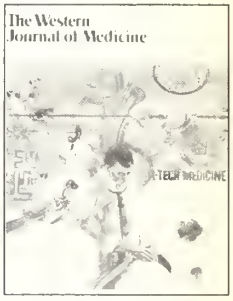

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In Memoriam

CORRECTION

In the August 1992 issue, page 125, it was erroneously reported that Ronald A. Griffin, MD, member of the San Bernardino County Medical Society, had died. The journal regrets the error and apologizes to Dr Griffin.

California Medical Association

BAGNALL, WILLIAM STANLEY, Richmond. Died Feb 9, 1992, aged 81. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, 1938. Licensed in California in 1939. Dr Bagnall was a member of the Alameda-Contra Costa Medical Association.

BOUILLON, VICTOR J., Napa. Died Aug 24, 1992, aged 68. Graduate of University of Washington School of Medicine, Seattle, 1953. Licensed in California in 1953. Dr Bouillon was a member of the Napa County Medical Society.

BOYLE, JOSEPH F., Washington, DC. Died Jul 16, 1992, aged 67. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania, 1948. Licensed in California in 1952. Dr Boyle was a member of the Los Angeles County Medical Association.

BRADSHAW, STANLEY P., Martinez. Died May 30, 1992, aged 78. Graduate of Stanford University School of Medicine, Stanford, California, 1941. Licensed in California in 1941. Dr Bradshaw was a member of the Alameda-Contra Costa Medical Association.

CADY, CARL F., Loma Linda. Died Feb 22, 1992, aged 76. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1958. Licensed in California in 1960. Dr Cady was a member of the San Bernardino County Medical Society.

CARSON, JOSEPH P., Palo Alto. Died Aug 17, 1992, aged 77. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1941. Licensed in California in 1954. Dr Carson was a member of the Santa Clara County Medical Association.

CHRISTMAN, ALBERT H., Portola Valley. Died Jul 22, 1992, aged 79. Graduate of University of Pittsburgh, Pittsburgh, Pennsylvania, 1937. Licensed in California in 1947. Dr Christman was a member of the San Diego County Medical Society.

CLARK, RICHARD N., Sherman Oaks. Died Feb 26, 1992, aged 77. Graduate of Stanford University School of Medicine, Stanford, California, 1944. Licensed in California in 1944. Dr Clark was a member of the Los Angeles County Medical Association.

COMPTON, ALFRED D., JR, Oakland. Died Jul 10, 1992, aged 80. Graduate of Cornell University Medical College, New York, New York, 1950. Licensed in California in 1957. Dr Compton was a member of the Alameda-Contra Costa Medical Association.

COTLER, GERALD, Encino. Died May 31, 1992, aged 59. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Cotler was a member of the San Diego County Medical Society.

CYR, GERALD A., Napa. Died Jul 5, 1992, aged 86. Graduate of Jefferson Medical School, Philadelphia, Pennsylvania, 1930. Licensed in California in 1958. Dr Cyr was a member of the Napa County Medical Society.

DYAR, ROBERT, Berkeley. Died Jul 25, 1992, aged 82. Graduate of University of Minnesota Medical School, Minneapolis, 1935. Licensed in California in 1949. Dr Dyar was a member of the Alameda-Contra Costa Medical Association.

FISH, ALBERT, San Carlos. Died Jul 1992, aged 72. Graduate of University of Illinois College of Medicine, Chicago, 1951. Licensed in California in 1952. Dr Fish was a member of the San Mateo County Medical Society.

FLOOD, ANTHONY J., JR, San Jose. Died Jul 11, 1992, aged 74. Graduate of Queens University, 1944. Licensed in California in 1962. Dr Flood was a member of the Santa Clara County Medical Association.

FRANK, DEE E., Los Angeles. Died Feb 28, 1992, aged 82. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1934. Licensed in California in 1943. Dr Frank was a member of the Los Angeles Medical Association.

GRAY, HAROLD F., JR, Gridley. Died Jun 8, 1992, aged 80. Graduate of Stanford University School of Medicine, Stanford, California, 1954. Licensed in California in 1954. Dr Gray was a member of the Butte-Glenn Medical Society.

GRIFFIN, RICHARD G., Loma Linda. Died Apr 1992, aged 59. Graduate of University of California, San Francisco, 1957. Licensed in California in 1960. Dr Griffin was a member of the San Bernardino County Medical Society.

HANNON, JOSEPH L., Salinas. Died Aug 6, 1992, aged 68. Graduate of St Louis University, St Louis, Missouri, 1948. Licensed in California in 1968. Dr Hannon was a member of the Monterey County Medical Society.

HARRINGTON, EILEEN S., Escondido. Died Feb 13, 1992, aged 85. Graduate of University of Utah School of Medicine, Salt Lake City, 1945. Licensed in California in 1949. Dr Harrington was a member of the San Diego County Medical Society.

HARRIS, JEROME S., Fresno. Died Jul 31, 1992, aged 74. Graduate of State University of New York, Brooklyn, 1943. Licensed in California in 1953. Dr Harris was a member of the Fresno-Madera Medical Society.

KERSHNAR, HARVEY E., Tustin. Died Jun 12, 1992, aged 49. Graduate of State University of New York, Brooklyn, 1968. Licensed in California in 1970. Dr Kershnar was a member of the Orange County Medical Association.

KLOTZ, NORMAN, San Francisco. Died May 25, 1992, aged 88. Graduate of University of California, San Francisco, 1930. Licensed in California in 1930. Dr Klotz was a member of the San Francisco Medical Society.

KNOBLOCH, JOSEPH D., Redlands. Died Jul 28, 1992, aged 84. Graduate of Harvard Medical School, Boston, Massachusetts, 1943. Licensed in California in 1963. Dr Knobloch was a member of the San Bernardino County Medical Society.

KRAUSE, HAZEL W., Del Mar. Died Feb 8, 1992, aged 83. Graduate of University of Manitoba, Canada, 1930. Licensed in California in 1957. Dr Krause was a member of the Los Angeles County Medical Association.

LANGE, OTTO H., Sherman Oaks. Died Jan 13, 1992, aged 77. Graduate of University of Southern California School of Medicine, Los Angeles, 1942. Licensed in California in 1942. Dr Lange was a member of the Los Angeles County Medical Association.

MITCHELL, CYRIL L., Oakhurst. Died Aug 8, 1992, aged 82. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1939. Licensed in California in 1939. Dr Mitchell was a member of the Fresno-Madera Medical Society.

NIES, ARTHUR J., Redlands. Died Jul 20, 1992, aged 88. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1932. Licensed in California in 1932. Dr Nies was a member of the Orange County Medical Association.

NORTHAM, ALLAN LESLIE, Napa. Died Jul 5, 1992, aged 68. Graduate of Tufts Medical School, Boston, Massachusetts, 1952. Licensed in California in 1954. Dr Northam was a member of the Napa County Medical Society.

PASSOFF, TODD L., Anaheim. Died May 8, 1992, aged 43. Graduate of Mt Sinai School of Medicine, New York, 1975. Licensed in California in 1979. Dr Passoff was a member of the Orange County Medical Association.

(Continued on Page 517)

In Memoriam

(Continued from Page 516)

RANSOM, DOW H., JR, San Jose. Died Jul 17, 1992, aged 74. Graduate of Washington University School of Medicine, St Louis, Missouri, 1942. Licensed in California in 1942. Dr Ransom was a member of the Santa Clara County Medical Association.

RUMSEY, JOHN M., San Diego. Died Jun 19, 1992, aged 80. Graduate of University of Kansas School of Medicine, Kansas City, 1936. Licensed in California in 1943. Dr Rumsey was a member of the San Diego County Medical Society.

SEAVERS, RAY, JR, San Bernardino. Died Jul 30, 1992, aged 73. Graduate of University of California, San Francisco, School of Medicine, 1943. Licensed in California in 1944. Dr Seavers was a member of the San Bernardino County Medical Society.

STEINER, PAUL, San Leandro. Died Apr 8, 1992, aged 82. Graduate of University of Illinois College of Medicine, Chicago, 1945. Licensed in California in 1948. Dr Steiner was a member of the Alameda-Contra Costa Medical Association.

WATT, JAMES Y., Newport Beach. Died Jul 21, 1992, aged 70. Graduate of University of Utah School of Medicine, Salt Lake City, 1946. Licensed in California in 1950. Dr Watt was a member of the Orange County Medical Association.

ZEFF, MAURICE, Oakland. Died Feb 21, 1992, aged 86. Graduate of University of California, San Francisco, School of Medicine, 1937. Licensed in California in 1937. Dr Zeff was a member of the Alameda-Contra Costa Medical Association.

New Mexico Medical Society

COLEMAN, TOBERT C., Portales. Died May 26, 1992, aged 77. Graduate of University of Colorado School of Medicine, Denver, 1951. Licensed in New Mexico in 1954. Dr Coleman was a member of the Curry-Roose County Medical Society.

MCKINNON, DANIEL A., Albuquerque. Died Aug 24, 1992, aged 83. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1939. Licensed in New Mexico in 1941. Dr McKinnon was a member of the Greater Albuquerque Medical Association.

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5. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages or other securities: There are no bondholders, mortgagees, or other security holders.
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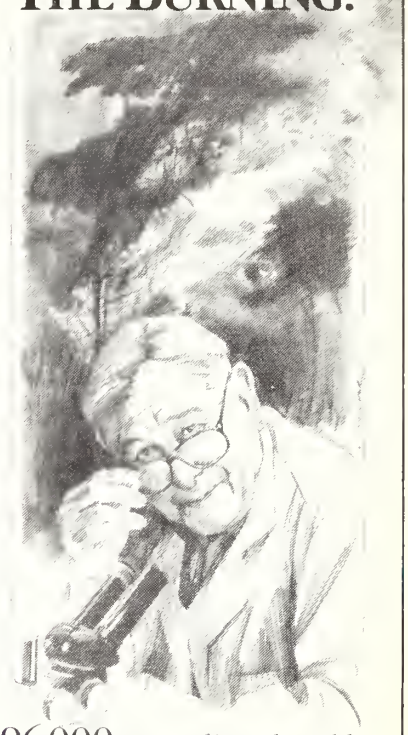
IT'S TIME TO STOP THE BURNING.



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The National Arbor Day Foundation

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ABSTRACTS NOVEMBER 1992

(Lazarus HM: Abdominal aortic aneurysm—Incidence in a hospital population at risk. West J Med 1992 Nov; 157:527-529)

The incidence of abdominal aortic aneurysms has been studied in various selected patient groups. In this study, 100 male patients on a cardiology service who were older than 60 years and over 170 cm (5 ft 7 in) tall were examined by abdominal ultrasonograms. A total of 11 aneurysms were found, 2 of which were more than 4.5 cm in diameter. Other abnormalities that were found included renal disease in 20 patients (1 carcinoma treated with a curative nephrectomy), gallbladder disease in 22 patients, and miscellaneous intra-abdominal disease in 6 patients; 47 patients had no abnormalities found. The aneurysms of these patients were classified by height in 5-cm (2-in) increments. No significant difference in the incidence of aneurysms was found within the groups, but these groups are small and a significant difference would not be expected. It is of interest that the two large aneurysms were in persons taller than 180 cm (5 ft 11 in). Previous ultrasonographic studies of aneurysmal incidence have not reported other intra-abdominal disease.

SMOKING PULMONARY DISEASE

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SMOKING PULMONARY DISEASE

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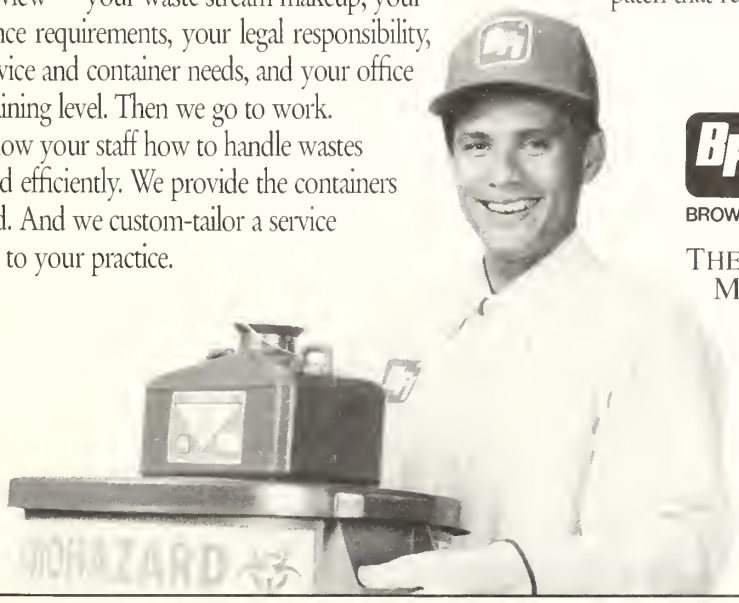

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CONTINUING MEDICAL EDUCATION

(Continued from Page 511)

ENDOCRINOLOGY/METABOLISM

February 19-20—**New Horizons in Diabetes Therapy.** Scripps Clinic and Research Foundation at Scripps Memorial Hospital, La Jolla. Fri-Sat. $175. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5—**19th Annual Diabetes Symposium.** UCD at Sheraton Sunrise, Rancho Cordova. Fri. 6 hrs. Contact: UCD.

March 10-11—**Advances in Endocrinology & Metabolism.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 12-13—**Diabetes Update.** UCSF at Ritz-Carlton Hotel, San Francisco. Fri-Sat. 11 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 12-14—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 12-15—**45th Annual Scientific Assembly.** California Academy of Family Physicians at Wyndham Hotel & Palm Springs Convention Center. Fri-Mon. 25.5 hrs. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

February 20—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium. Sat. 6 hrs. Contact: UCD.

March 24-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Fri. 15.5 hrs. $300. Contact: UCSF, Department of Family and Community Medicine.

April 10-17—**Primary Care Medicine: Update 1993.** UCSF at Maui Inter-Continental Hotel, Wailea, Hawaii. 1 week. 20 hrs. $545. Contact: UCSF.

April 22-24—**Rheumatology for Primary Care Physicians.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 14 hrs. Contact: UCSF.

April 22-25—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

January 19-22—**Intensive Course in Geriatric Medicine.** UCLA at Ritz-Carlton Hotel, Marina del Rey. Tues-Fri. 29 hrs. $625. Contact: UCLA.

February 5-6—**Alzheimer's Disease New Advances in Treatment.** UCSD at San Diego. Fri-Sat. Contact: UCSD.

HEMATOLOGY

December 4—**Current Issues in Hemophilia Care.** Orthopaedic Hospital Los Angeles at Hyatt Regency Alicante, Anaheim. Sat. 6 hrs. $100. Contact: Hemophilia Care, Meeting Management, 5665 Oberlin Dr, #110, San Diego 92121. (619) 453-6222.

February 14-17—**Clinical Hematology and Oncology: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sun-Wed. 18 hrs. $385. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 17-20—**5th International Symposium on Blood Substitutes.** UCSD at Sheraton Harbor Island. Wed-Sat. Contact: UCSD.

INFECTIOUS DISEASES

November 16-20—**Advanced STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Fri. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

November 30-December 4—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Fri. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

December 14-15—**Clinical Care of the AIDS Patient.** UCSF at Sheraton Palace Hotel, San Francisco. Mon-Tues. 13 hrs. $250. Contact: UCSF.

January 5-7—**Part-time Intensive Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

January 12-23—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1½ weeks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

February 5-6—**11th Annual Practical Update of Infectious Diseases.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. 12 hrs. $160. Contact: UCD.

April 28-30—**Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. Contact: UCSF.

INTERNAL MEDICINE

January 30-February 1—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Sat-Mon. Contact: UCSD.

February 5-7—**State of the Art Urology.** UCLA at Ritz-Carlton, Marina del Rey. Fri-Sun. Contact: UCLA Extension.

February 6—**California Association of Cytology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

February 20-25—**Topics and Advances in Internal Medicine.** UCSD at Hyatt Regency. Sun-Thurs. Contact: UCSD.

March 19-25—**Internal Medicine 1993: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Tues. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

NEUROLOGY

February 4-6—**16th Annual: Neurology for Non-Neurologists.** UCSD at Doubletree Hotel Horton Plaza, San Deigo. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 11-13—**26th Annual Recent Advances in Neurology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 15 hrs. $345. Contact: UCSF.

OB/GYN

December 3-5—**Obstetrics and Gynecology Conference.** University of Nebraska Medical Center at Bally's, Las Vegas. Thurs-Sat. $250. Contact: Brenda Ram, 600 S 42nd St, Omaha, NE 68198-5651. (402) 559-4152.

January 17-19—**Annual Ambulatory Gynecology Update: 1993.** UCD at Incline Village, Nevada. Sun-Tues. 14 hrs. $260. Contact: UCD.

February 11-14—**48th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: C. James Dowden, OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 17-19—**Contemporary Obstetrical & Transvaginal Ultrasound.** UCSD. Wed-Fri. Contact: UCSD.

March 13—**Women's Health Issues.** UCD at Cancer Center Auditorium. Sat. Contact: UCD.

April 14-18—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Susan Butler, PCFS, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 25-February 5—**Occupational & Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. 1½ weeks. 80 hrs. $1400. Contact: UCSF.

February 8-12—**Occupational & Environmental Medicine: Session III.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

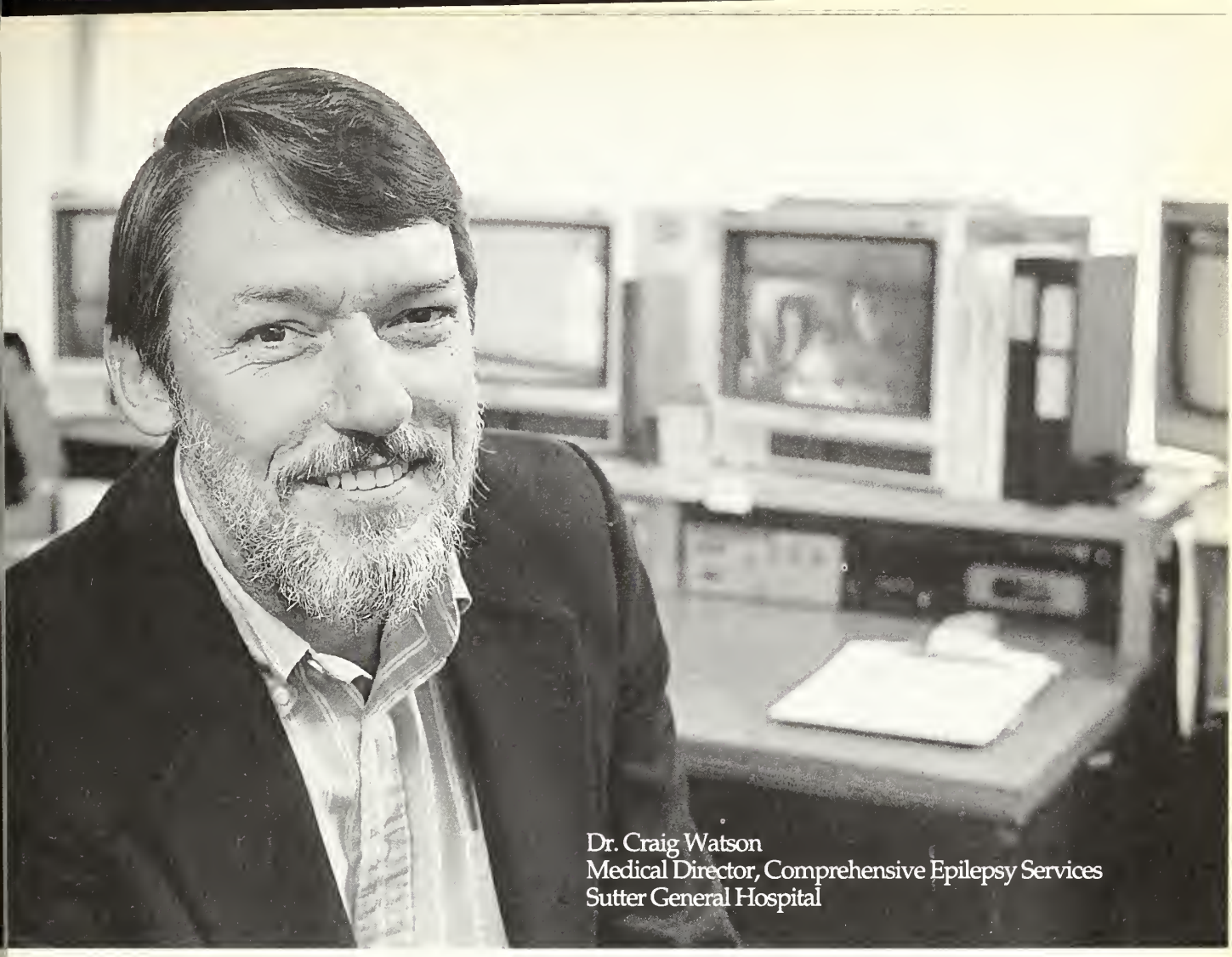
ONCOLOGY

March 4-5—**Dimensions of Caring 1993: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Doubletree Hotel Horton Plaza, La Jolla. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-9592.

OPHTHALMOLOGY

January 30—**Genetic Disease and the Eye.** Cedars Sinai Medical Center Division of Ophthalmology at Ma Maison Hotel, Los Angeles. Sat. 8 hrs. $50. Contact: Yaron Rabinowitz, MD, 444 S San Vicente Blvd, Ste 600, Los Angeles 90048. (310) 855-2613.

(Continued on Page 522)



Dr. Craig Watson
Medical Director, Comprehensive Epilepsy Services
Sutter General Hospital

YOU CAN'T WATCH YOUR EPILEPSY PATIENTS ROUND-THE-CLOCK. BUT WE CAN.

Even if you've made a positive diagnosis of epilepsy in patients who are suffering from seizures, the most effective treatment is sometimes elusive.

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For more about services or patient transfers, call Sutter Neuroscience Center at Sutter General Hospital in Sacramento, (916) 455-4323.

Sutter Neuroscience Center

(Continued from Page 520)

ORTHOPEDICS

November 19-21—**San Diego Spine Symposium.** UCSD at San Diego Marriott. Thurs-Sat. 11 hrs. Contact: UCSD.

December 3—**9th Annual Symposium on Common Musculoskeletal Problems: Current Concepts in Diagnosis and Management of Arthritis.** VA Medical Center Sepulveda. Thurs. 6 hrs. Contact: Arun Mehta, MD, VA Med Ctr, RMS 117, Sepulveda 91343-2036. (818) 895-9344.

December 9-13—**Fall Symposium on Back Pain.** American Back Society at Hyatt Regency Embarcadero, San Francisco. Wed-Sun. Contact: ABS, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

OTOLARYNGOLOGY

November-April 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Mon-Sat. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

PATHOLOGY

March 13—**Update on Dialysis Access: Creation, Maintenance & Salvage.** UCSD at Le Meridien. Sat. Contact: UCSD.

April 17—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-6310.

PEDIATRICS

January 26-30—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Hyatt Regency, La Jolla. Tues-Sat. 28 hrs. Contact: Center for Child Protection, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4950.

February 15-17—**Pediatrics Update.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

February 26-28—**Current Concepts in Pediatric Medicine: 1993.** Children's Hospital San Diego and American Academy of Pediatrics at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Continuing Education, 8001 Frost St, San Diego 92123. (619) 576-4072.

April 3-10—**Pediatrics Emergencies.** UCSD at Poipu Beach Hotel & Waiohai Resort, Kauai, Hawaii. 1 wk. 21 hrs. $450. Contact: UCSD.

PSYCHIATRY

January 24-29—**19th Annual Midwinter Program for Psychiatrists: Special Focus on Hysteria.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 12-14—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Catamaran Hotel, San Diego. Fri-Sun. Contact: UCSD.

February 27—**Sleep Apnea: New Insights into Pathophysiology and Treatment.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 4-6—**51st Annual Meeting of the American Psychosomatic Society.** UCSD at Omni Hotel, San Diego. Thurs-Sat. Contact: UCSD.

RADIOLOGY

December 28-January 2—**Year End Review of Imaging and Intervention.** UCSD at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Sat. 25 hrs. $550-$595. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 15-17—**45th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.75 hrs. $125-$450. Contact: LARS, MWRC, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078.

January 16-17—**Interventional Radiology Update.** Stanford University at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 7.5 hrs. $200-$250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 18-20—**Neuroradiology Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 17.5 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 21-24—**Breast Imaging Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 17.25 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 15-19—**Diagnostic Imaging Update: Mammography, MRI, Body Imaging, Neuroradiology, Pediatrics.** Stanford University Medical Center at Ritz-Carlton, Palm Beach. Mon-Fri. 23.75 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 22-26—**Diagnostic Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Kapalua Bay, Maui, Hawaii. Mon-Fri. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

March 8-12—**8th Annual San Diego Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 29 hrs. $595. Contact: Dawne Ryals, PO Box 1925, Roswell 30077-1925. (404) 641-9773.

March 10-12—**13th Annual Radiation, Oncology, Biology & Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: Crest Organization (415) 595-2704.

March 28-April 2—**General Radiology Review Course.** UCLA at Doubletree Hotel, Marina del Rey. Sun-Fri. 40 hrs. $425. Contact: UCLA Department of Radiological Sciences.

April 18-23—**13th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $445. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 24—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8.25 hrs. $135. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

January 8-9—**15th Annual Postgraduate Course: What's New in General Surgery.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 15 hrs. $285. Contact: UCD.

January 24-29—**16th Annual Postgraduate Assembly in Surgery.** UCSD at Doubletree Hotel, Horton Plaza, San Diego. Sun-Fri. Contact: UCSD.

March 17-20—**Surgical Challenges of the Head & Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at CMG Building, La Jolla. Wed-Sat. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

December 24-29—**Advances in Medicine '92.** Hawaii Medical Association at Kaanapali Beach, Maui, Hawaii. Fri-Wed. 16 hrs. $450. Contact: Joe Harrison, MD, PO Box 833, Makawao, HI 96768. (808) 878-7657.

January 8-10—**The Medical Office Laboratory Conference.** SDSU at San Diego Red Lion Hotel, Fri-Sun. 20 hrs. $425. Contact: Anne Wright, (619) 594-6255.

January 22-23—**Nutritional Medicine in Medical Practice: Putting Nutrition to Work in the Prevention and Treatment of Common Diseases and Chronic Conditions.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Sat. 14 hrs. $165. Contact: UCLA Extension.

February 22-26—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

March 26-April 4—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. 1½ wks. Contact: UCLA Extension.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology & Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

(Continued on Page 524)

1993

Western Scientific Assembly

ANNUAL SESSION

Mark your February calendar for CMA's premier educational event!

February 26-March 3, 1993
Disneyland Hotel, Anaheim

Featured will be dozens of programs, showcasing some of the finest medical educators California has to offer. And the variety of clinical topics literally spans the medical and surgical spectrum.

This year's rich and varied topics include: management of pain, screening technologies and controversies, sleep disorders, skin problems of active patients, sports injuries of the brain and spine, new standards for blood-borne pathogens and CLIA, orthopedic update on the foot and ankle, ophthalmologic issues for primary care, treatment of rhinitis and sinusitis, common office gynecological problems, professional liability issues in breast cancer and implants, imaging choices 1993, management of common pediatric problems, carpal tunnel syndrome, management of difficult wound problems, HIV prevention, detection and early management, algorithms for alcoholics, management of "difficult" patients, tobacco intervention for special populations, disruptive physicians and the dilemmas for medical staff, residency selection and career planning, new frontiers in family medicine, workshops on cardiac life support and the suture course. **This is a great opportunity to earn CME Category I credit!**

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Name _____

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City _____

State _____ Zip _____

(Continued from Page 522)

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

November 19-22—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sun. Contact: Pat Winter, (303) 861-6668.

November 30-December 4—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Fri. Contact: Jeff Griebel, (303) 861-6188.

January 11-15—**Twenty-Fourth Annual Cardiovascular Conference at Snowmass.** American College of Cardiology at the Convention Center, Snowmass Resort, Snowmass. Mon-Fri. Contact: Margaret Sgro, American College of Cardiology, (800) 257-4739.

January 22-24—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs Medical Center at Beaver Run Resort and Conference Center, Breckenridge. Fri-Sun. Contact: Victoria Hall or Karen Babcock, (303) 393-2826, or FAX (303) 393-4656.

January 23-30—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Tamarron Resort, Durango. Sat-Sat. Contact: U of Colo.

February 22-26—**Colorado Conference on Contemporary Family Practice.** University of Colorado School of Medicine at Breckenridge. Mon-Fri. Contact: U of Colo.

February 27-March 5—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Vail. Sat-Fri. Contact: U of Colo.

February 27-March 6—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Sat. Contact U of Colo.

February 28-March 5—**ENT Ski Conference.** University of Nebraska Medical Center Continuing Medical Education Program at Keystone Resort, Keystone. Sun-Fri. Contact: Brenda C. Ram, University of Nebraska Continuing Education, (402) 559-4152.

March DTBA—**Fifth Annual Colorado Geriatrics Overview.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. Contact: U of Colo.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

December 3-5—**American College of Physicians, New Mexico Chapter, Annual Scientific Meeting.** Marriott Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM

December 11-12—**Trauma Update 1992.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131, (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

November 20-21—**Pediatric Update.** PCMC at Holiday Inn, St George. $100. Fri-Sat. Contact: PCMC (Pediatric CME).

February 8-12—**Advances in Internal Medicine.** UUSM at Snowbird, Mon-Fri. Contact: UUSM.

February 12-13—**Utah Ophthalmology Society—Annual Winter Ski Meeting—Ski '93.** Fri-Sat. Contact: UOS.

January 14—**Pediatric Topic.** Thurs. Contact: UOS.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

(Continued on Page 525)

(Continued from Page 524)

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

November 20—**Orthopaedic Trauma Update.** Spokane. Fri. Contact: U/W.

November 20—**GI Day.** Seattle. Fri. Contact: PCMS CME.

December 3—**Arthrocentesis & Injection Techniques.** Seattle. Thurs. Contact: U/W.

December 4—**Nuts, Bolts, and Innovation in Gastrointestinal Disease.** Tacoma. Fri. Contact: PCMS CME.

December 4—**Rehabilitation Issues in Aging.** Seattle. Fri. Contact: U/W.

December 4-5—**Urology Annual Meeting.** Vancouver, BC. Fri-Sat. Contact: NWUS, (206) 441-9762.

December 10-11—**ACLS Course.** Tacoma. Thurs. Contact: PCMS CME.

December 10-12—**8th Infectious Disease Conference.** Thurs-Sat. Everett. Contact: PNMEI, (206) 258-6322.

December 10-12—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 10-12—**Internal Medicine Annual Meeting.** Seattle. Thurs-Sat. Contact: Washington State Society of Internal Medicine, (206) 441-9762.

December 12—**Cardiology FPs.** Tacoma. Sat. Contact: Multicare, (206) 594-1221.

December 15-16—**Introduction to Industrial Hygiene.** Seattle. Tues-Wed. Contact: Northwest Center for Occupational Health & Safety, (206) 543-1069.

January 7—**Community Air Quality.** Seattle. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 15-17—**WTS Chest Conference & Lung Day.** Leavenworth. Fri-Sun. Contact: Washington Thoracic Society, (206) 441-5100.

January 21—**Law & Medicine Symposium.** Seattle. Thurs. Contact: PCMS CME.

January 27—**Oncology Update.** Tacoma. Tues. Contact: Multicare, (206) 594-1221.

January 28-29—**Psycho-social & Neuropsychiatric Aspects of AIDS.** Seattle. Wed-Thurs. Contact: U/W.

February 3—**HIV Infections.** Tacoma. Wed. Contact: PCMS CME.

February 4-6—**Mt. Bachelor—CME.** Bend, Oregon. Thurs-Sat. Contact: PCMS CME.

February 11—**Managing Occupational Health and Safety Programs.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

February 12—**General Surgery Review.** Everett. Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

February 26—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

March 2—**Health Effects of Noise Exposure.** Seattle. Tues. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 3-6—**North Pacific Pediatric Society.** Seattle. Wed-Sat. Contact: Children's, (206) 526-2501.

March 11—**Neurotoxicology.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 11-12—**Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 12—**Pulmonary Medicine for the Family Practitioner.** Seattle. Fri. Contact: Children's, (206) 526-2501.

March 19-20—**APLS Course.** Seattle. Fri-Sat. Contact: Washington Chapter, American College of Emergency Physicians.

March 24-26—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 26-27—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: Washington Academy of Eye Physicians and Surgeons, (206) 441-9762.

April 6-9—**Family Practice Review.** Arizona. Tues-Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

April 9—**Advances in Occupational and Environmental Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 16—**20th Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 16-17—**Tacoma Surgical Club.** Tacoma. Thurs-Fri. Contact: PCMS CME.

April 23—**Terminal/Palliative Care Update.** Tacoma. Fri. Contact: PCMS CME.

April 23-25—**Washington State Physical Therapy Association.** Seattle. Fri-Sun. Contact: Children's, (206) 526-2501.

April 28-30—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Fri. Contact: Washington Chapter, American College of Emergency Physicians, (206) 441-9762.

April 30-May 2—**Radiology Annual Meeting.** Vancouver, BC. Fri-Sun. Contact: Pacific Northwest Radiological Society, (206) 441-9762.

May 7—**Office Gynecology.** Tacoma. Fri. Contact: PCMS CME.

May 7-8—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

May 13—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 16-19—**American Thoracic Society.** San Francisco. Sun-Wed. Children's, (206) 526-2501.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare, (206) 592-1221.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104 (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898. ◆

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Articles

Abdominal Aortic Aneurysm
Incidence in a Hospital Population at Risk

HARRISON M. LAZARUS, MD, *Salt Lake City, Utah*

The incidence of abdominal aortic aneurysms has been studied in various selected patient groups. In this study, 100 male patients on a cardiology service who were older than 60 years and over 170 cm (5 ft 7 in) tall were examined by abdominal ultrasonograms. A total of 11 aneurysms were found, 2 of which were more than 4.5 cm in diameter. Other abnormalities that were found included renal disease in 20 patients (1 carcinoma treated with a curative nephrectomy), gallbladder disease in 22 patients, and miscellaneous intra-abdominal disease in 6 patients; 47 patients had no abnormalities found. The aneurysms of these patients were classified by a patient's height in 5-cm (2-in) increments. No significant difference in the incidence of aneurysms was found within the groups, but these groups are small and a significant difference would not be expected. It is of interest that the two large aneurysms were in persons taller than 180 cm (5 ft 11 in). Previous ultrasonographic studies of aneurysmal incidence have not reported other intra-abdominal disease.

(Lazarus HM: Abdominal aortic aneurysm—Incidence in a hospital population at risk. West J Med 1992 Nov; 157:527-529)

The incidence of abdominal aortic aneurysms has been studied in various selected patient groups. These have included patients with hypertension,[1] peripheral vascular disease,[2] heart disease,[3] a family history of abdominal aortic aneurysm,[4] and from a general patient population.[5]

This study deals with inpatients on a cardiology service, consisting of men who were older than 60 years and who also were taller than 170 cm (5 ft 7 in), to determine the prevalence of aortic aneurysms. Aneurysms have been described as the "U-boat inside the belly . . . and like them they can be found by reflected sound waves and taken out before they torpedo the patient."[6] We wished to determine the yield of an ultrasound examination of the abdominal aorta in a patient population that was suspected to be at high risk. We knew that we would be able to screen only a small number of patients in this pilot study so these criteria, which may exclude some patients with aneurysms, were chosen. In this small initial study, we ran the risk that the incidence of aneurysmal findings could be zero. We were, however, anticipating an incidence of about 5%.

Patients and Methods

Patients who were admitted for cardiac evaluation were considered for the study. This study was limited to men to increase the incidence of a positive result from the screening study because men have a 6:1 incidence over women of abdominal aortic aneurysms.[7] To qualify for the study, a patient had to be age 60 years or older, as abdominal aortic aneurysms become a problem only after the fifth decade of life.[8] Also, only men above 170 cm (5 ft 7 in) in height were studied based on findings that patients with aneurysmal disease were 5 cm (2 in) taller than those of similar age with occlusive vascular disease.[9] The patients had their abdominal ultrasound procedure done while they were in the hospital for their cardiology evaluation. A standard evaluation of the abdominal aorta was carried out using GE 3600, Toshiba SSA-270A, and Acuson 128 instruments and was supplemented by images of other intra-abdominal organs—including the inferior vena cava, liver, spleen, gallbladder, biliary tree, kidneys, and pancreas—in accordance with American College of Radiology standards and guidelines for doing abdominal ultrasonographic examinations.* The diagnosis of abdominal aortic aneurysm was made when focal aortic enlargement was observed interrupting the normal tapering of the aorta as it was imaged proximally to distally.

Results

The results of the 100 patients studied are shown in Table 1. In all, 11 aneurysms were found, with a 95% confidence level by two-tailed analysis of 5.62 to 18.83. Two of the aneurysms were greater than 4.5 cm in diameter, and nine were smaller than 4.5 cm. In addition, other pathologic abnormalities were found during the ultrasound examination. Renal disease was found in 20 patients, 1 being a renal cancer that was subsequently treated with a curative nephrectomy. Gallbladder disease was found in 22 patients, miscellaneous intra-abdominal disease in 6, and in only 47 patients were no abnormalities found. None of these patients had any abdominal symptoms, signs, or physical findings of the disorder detected. No significant differences in the groups in each five-year interval were found; however, these groups are too small to expect significance.

The aneurysms of these patients were further classified by the patients' height in 5-cm (2-in) increments. It is of interest that the only two large aneurysms were in persons over 180 cm (5 ft 11 in) tall.

Discussion

Abdominal aortic aneurysms in the United States are the 15th leading cause of death, killing more than 15,000 Americans each year.[10] This death is from a lesion that can be eliminated if the aneurysm is found and treated. The operative mortality of an elective aneurysm repair is 5% or more,[11]

*D. C. Hardy, MD, and T. G. Lee, MD, performed the ultrasound studies.

From FHP Health Care, LDS Hospital and the University of Utah, School of Medicine, Salt Lake City.
This study was supported by a grant from the LDS Hospital-Deseret Foundation.
Reprint requests to Harrison M. Lazarus, MD, 853 13th Ave, Salt Lake City, UT 84103.

TABLE 1.—*Ultrasonographic Results in Each 5-Year Age Group in 100 Men 60 Years of Age and Older**

Ultrasonographic Findings	Age, years 60-64 n=20	65-69 n=31	70-74 n=27	75-79 n=11	≥ 80 n=11	Total
Abdominal aortic aneurysm						
> 4.5 cm	1	1	0	0	0	2
< 4.5 cm	1	2	3	2	1	9
Renal	1	6	6	4	3	20
Gallbladder	5	9	6	1	1	22
Hepatic	1	1	2	0	0	4
Miscellaneous	0	1	1	1	0	3
Negative	11	14	10	5	7	47

*The numbers in the columns are the number of patients in each age group in whom lesions or abnormalities were found

whereas the operative mortality for aneurysms once they have ruptured is 50%.[12] Untreated ruptured abdominal aortic aneurysms are almost uniformly fatal.[13] Johansson and Swedenborg found the actual community incidence of mortality from ruptured aortic aneurysms to be 94%.[14] The percentage of patients with ruptured aneurysms who die of their aneurysm is in the range of 80% to 95%.[11]

An abdominal aortic aneurysm is a lethal disease, requiring that this "U-boat" be found early on, and the best way for detection so far is by ultrasonography. Aortic aneurysms usually are an incidental finding, but they also may suddenly rupture with no previous symptoms. Clinical examination is unreliable, missing half of the aneurysms found by ultrasonogram, and the clinical suspicion of an aneurysm is 3½ times more likely to be wrong than right.[15] It is well recognized that even small aneurysms stand a substantial chance of rupture within a few years. Darling and co-workers stated that aneurysms 4 to 7 cm in diameter have a 25% chance of rupture, and those less than 4 cm in diameter have a 9.5% chance of rupture.[16] Conenwett and associates reported a rupture rate of 6% per year for small aneurysms.[17]

Therefore, it is important that aneurysms be detected before they become symptomatic or rupture. A policy for small aneurysms or ectatic aortas is to observe them every six months with clinical and ultrasound examinations. If an aneurysm becomes symptomatic or rapidly enlarges, an operation is indicated. Although most vascular surgeons would operate on aneurysms larger than 5 cm, there is no consensus as to when an operation is needed on smaller ones.

Screening of the general population is perhaps not feasible due to the large numbers involved; a policy of screening high-risk groups could be cost-effective, however. The incidence of abdominal aneurysms in the older general population is 2% to 3% as defined by autopsy studies.[18] The incidence of aneurysms increased sevenfold between 1951 and 1980. The greatest increase occurred in small asymptomatic and uncomplicated aortic aneurysms.[19] Not only is the incidence increasing, but the number of deaths from abdominal aortic aneurysms was found to increase in the three decades from 1954 to 1984. The annual increase in the number of deaths in the early period was 15% and continued to increase at 4½% annually in the last decade.[20] The incidence of abdominal aneurysms will continue to increase as our population ages.

Of the 11 aneurysms identified in this study, only 2 were large enough to require surgical intervention; however, because it is known that small aneurysms can rupture and will grow, these cannot be ignored. Because patients with small aortic aneurysms are usually asymptomatic, some laboratory method must be used. Abdominal ultrasonography seems to be the best method now available for such detection, being safe, rapid, and highly accurate with a detection rate approaching 100%.[21] Small aneurysms can be monitored with ultrasonograms at regular intervals and surgically repaired after there are symptoms or growth beyond a certain measure. Criteria for whether to choose a follow-up study versus recommending elective surgical repair for all aneurysms, regardless of size, have not been established. Early diagnosis is obviously essential to either strategy. Once an aneurysm is detected the decision of whether to proceed with elective repair or with frequent follow-up with ultrasonograms must be made between the patient and physician. It has been stated that an ultrasound examination of the abdominal aorta done routinely as part of a health package for persons older than 50 years and repeated every five years when normal would go a long ways toward preventing the suffering caused by this common and terrible disease.[6] The rupture of an individual aneurysm cannot be predicted, and the evidence that the risk increases as the diameter of the aneurysm increases is incontrovertible.

The cost of an ultrasound study varies from $50 to $200 with a yield of about 1% to 5%. The cost-benefit ratio would be higher than the yield found with mammography screening. The number of deaths that can be prevented with aneurysm screening is about 30 times that which are prevented with a breast screening program.[22] To be cost-effective, screening must be directed at the population at greatest risk and still young enough to benefit from elective surgical treatment. The yield will be higher for men than for women. The male-to-female ratio of ruptured aneurysms in the 60- to 64-years age group is 11:1, 65 to 69 years is 10:1, 70 to 74 years is 7:1, 75 to 79 years is 6:1, 80 to 84 years is 4:1, and 85 to 89 years is 3:1.[20] We chose age 60, but age 50 or 55 may prove to be as useful. We had a height selection based on a patient with an aneurysm being 5 cm (2 in) taller than a patient with occlusive vascular disease.[9] Additional studies are needed on the relevance of this point.

This study points out the value of an ultrasonogram in men older than 60 years as a part of a regular health maintenance program. We were able to locate two large abdominal aortic aneurysms and nine smaller ones in this group of patients. In addition, we found a high yield of other diseases including an early renal cancer; 53% of the patients had intra-abdominal abnormalities identified.

Other ultrasound studies for aneurysms have not reported other intra-abdominal disorders.[1-6] These reports point out the high yield of valuable information on abdominal aneurysms only.

From performing abdominal ultrasound examinations in men older than 55 years, Collin concluded that 120 lives would be saved from aneurysmal rupture for every 10,000 ultrasonograms done.[22] The number of lives saved compares with the 4 lives saved for every 10,000 mammography examinations done. With additional abnormalities identified, the usefulness of abdominal ultrasonography in men older than 60 increases. Any cancers found would pay immediate dividends for the unsuspecting person. Although the knowledge of other findings, such as cholelithiasis,[23] does not demand immediate therapy, future complaints relevant to a known diagnosed abnormality will expedite treatment when the condition becomes symptomatic.

Thurmond and Semler studied a group of cardiology patients and found a 6.7% incidence of aneurysms greater than 4 cm in diameter in a group of 90 men older than 50 years.[3] It has been well accepted that aneurysms are rare in persons younger than 50 years, and few deaths occur from ruptured aneurysms before the age of 60.[13]

Collin and colleagues concluded that if ultrasonographic screening programs were extended to England and Wales, they would be expected to identify 52,500 men with abdominal aortic aneurysms. If elective surgical replacement of the aneurysms was done for 60% of the aneurysms 4 cm or more in diameter, 6,000 unnecessary deaths from aortic rupture would be prevented.[15] Aneurysms can be detected easily, inexpensively, and reliably by ultrasonogram, taking less than five minutes. Men older than 65 years in a totally noninvasive study have a positive finding rate higher than for most other routine investigations,[20] so this should be regarded as a standard part of the examination of elderly men. Having aortic aneurysm surveillance programs for high-risk populations and educating primary care physicians that most patients with abdominal aortic aneurysms can tolerate repair might substantially improve the natural history of this common and lethal disease.

Acknowledgment

The following physicians and their patients participated in this study: J. Anderson, MD, J. Brewerton, MD, J. L. Burke, MD, R. Fowles, MD, C. Haws, MD, S. Horton, MD, D. Lappé, MD, J. A. Laser, MD, R. Mackie, MD, H. W. Marshall, MD, J. Osborn, MD, M. Preece, MD, D. Richards, MD, D. Ridges, MD, D. Robinson, MD, G. Robinson, MD, S. Sorensen, MD, G. M. Vincent, MD, and K. Walsh, MD. T. Hansen, RN, helped in enlisting patients.

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Articles

Radiation Retinopathy

RONALD W. ZAMBER, MD, *and* JAMES L. KINYOUN, MD, *Seattle, Washington*

Radiation therapy is effective against many cancerous and noncancerous disease processes. As with other therapeutics, side effects must be anticipated, recognized, and managed appropriately. Radiation retinopathy is a vision-threatening complication of ocular, orbital, periorbital, facial, nasopharyngeal, and cranial irradiation. Factors that appear important in the pathogenesis of radiation retinopathy include total radiation dosage, fraction size, concomitant chemotherapy, and preexisting vascular disorders. Clinical manifestations of the disorder include macular edema and nonproliferative and proliferative retinopathy, similar to changes seen in diabetic retinopathy. Argon laser photocoagulation has proved efficacious for managing macular edema and fibrovascular proliferation in some of these patients.

Ongoing basic laboratory and clinical research efforts have led to a better understanding of the pathogenesis, natural history, and treatment response of radiation retinopathy. The ultimate goal of this knowledge is to improve the prevention, recognition, and management of this vision-threatening complication.

(Zamber RW, Kinyoun JL: Radiation retinopathy. West J Med 1992 Nov; 157:530-533)

On November 8, 1895, Wilhelm Röntgen availed to the world new and powerful diagnostic and therapeutic potential with his discovery of x-rays. Remarkably, within two months of Röntgen's discovery, a patient with cancer of the breast began receiving daily radiation treatment administered by Chicago medical student Emil Grubbé.[1] As greater understanding of the nature, power, and possible pathogenicity of x-rays emerged, refinements in delivery techniques evolved. In 1922 Claudius Regaud and Henri Contard developed fractionation techniques that greatly reduced the side effects of radiotherapy.[1] In the 1930s and 1940s, "super voltage" and "megavoltage" units were produced in the United States,[1] and the evolution and development of radiotherapy accelerated to become a fundamental cornerstone of cancer treatment.

The retinopathic effects of radiation exposure have been recognized for more than 50 years, dating back to Stallard's initial description in 1933.[2,3] He reported the occurrence of radiation retinopathy following radon seed treatment of retinoblastoma. Three to six weeks after irradiation, Stallard noted retinal hemorrhages and exudates in a circinate pattern followed by the development of disc edema, vascular sheathing, and ultimately optic atrophy. Because ionizing radiation is being used more frequently for many ocular, orbital, periorbital, and intracranial disease processes, radiation retinopathy continues to be a sight-threatening complication of radiation treatment despite technologic advances in radiation delivery and dosage calculations.

Studies of the retinal vaso-occlusive complications following ionizing radiation are especially enlightening because of this disorder's similarity to the retinal vascular abnormalities seen in other ocular and systemic diseases, particularly diabetes mellitus.[4-14] In addition, the vascular abnormalities consequent to radiation treatment ultimately may lead to severe visual impairment or blindness as in diabetic retinopathy. Thus, insightful analysis of clinical and laboratory studies of radiation retinopathy and its treatment may yield important information relevant to other ischemic and vasoproliferative retinal vascular disorders.

Pathogenesis

Radiation retinopathy has been reported following local irradiation with cobalt 60 plaques and external beam irradiation with megavoltage linear accelerators for the treatment of retinoblastoma,[4,15] choroidal melanoma,[4,5,7] choroidal metastases from breast carcinoma,[16] nasopharyngeal carcinoma and paranasal sinus tumors,[4,6,11,17-19] periorbital basal cell carcinoma,[11] Graves' ophthalmopathy,[9,20-22] and intracranial lesions[4,6,12,23,24] and following prophylactic cranial irradiation in patients with leukemia.[25] Typical radiation retinopathic changes also have been reported in 50% of survivors of the atomic bombing of Hiroshima and Nagasaki.[26]

Although 3,500 cGy had previously been accepted as the upper limit of safe total dosage,[27] cases of radiation retinopathy have been reported after much lower levels of irradiation. Doses as low as 1,100 cGy,[24] 1,200 cGy,[25] 1,700 cGy,[28] 2,000 cGy,[9,21] and 2,080 cGy[22] have resulted in radiation retinopathy. Patients seem to vary considerably with respect to susceptibility for retinal complications of radiation exposure; however, there is no question that increased radiation dosage increases the likelihood of retinal injury.[8,18,19,21,23,27,29] De Schryver and co-workers reported that patients receiving 2,500 cGy or more had a much higher incidence of retinal complications than patients receiving less than 2,500 cGy.[29] Shukovsky and Fletcher reported that nine of ten eyes in patients receiving more than 6,800 cGy suffered complete loss of vision[19]; the loss of vision was attributed to proliferative retinopathy in six eyes and to profound optic nerve atrophy in the other three eyes. In addition, Howard noted that patients receiving a second course of radiotherapy to their eyes for retinoblastoma suffered a more severe radiation retinopathy.[30] Reports also suggest that higher doses of local radiation therapy, as compared with external beam, must be given to produce radiation retinopa-

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thy.[4,31] Increased dosage, however, whether given locally or with external beam, does not necessarily cause the radiation retinopathy to develop sooner.[4,8,12,19]

Several studies have shown that increased fraction size correlates with an increased incidence of retinal complications.[4,6,21,22,27] The concomitant administration of chemotherapy also increases the risk of visual complications,[4,6,12,18,25,27] potentiates the development of radiation retinopathy at lower radiation doses,[25] and may shorten the latent period between exposure and retinal changes.[4,12,18,25] The total elapsed time in the course of irradiation also may be a risk factor for the development of radiation retinopathy.[27] Patients with a concomitant systemic disease—such as hypertension, diabetes mellitus, and autoimmune disorders—probably also are more susceptible to the retinal complications of radiation treatment.[4,6,27,32]

Histopathology

The retinopathic effects of irradiation may be classified as acute or chronic. Histologic studies of monkey eyes by Cibis and Brown suggest that acute changes (within six hours) include nuclear pyknosis, predominantly among rods, and edema restricted to outer retinal layers.[33] The chronic changes of radiation retinopathy in humans have been described extensively. The fundamental abnormality of chronic radiation damage is endothelial cell injury,[8,34-36] primarily in capillaries, followed by capillary closure (demonstrable with fluorescein angiography),[5,37,38] subsequent retinal ischemia, necrosis of nerve tissue, and fibrovascular proliferation.[4,6,8,9,36]

Histologic studies of human eyes by Egbert and associates have shown pronounced thickening of retinal arteriolar and capillary walls due to an accumulation of a fine, fibrillary "material."[34] Irvine and Archer and colleagues have described an apparent preferential loss of endothelial cells early in the pathologic process.[8,35,36] This differs from diabetic retinopathy in which pericytes reportedly disappear first.[8,35,39] Also, in contrast to diabetic retinopathy, microaneurysms and capillary hypercellularity were relatively less common among specimens showing radiation retinopathy,[8,36] and neovascularization has experimentally remained confined to the retina and choroid, without intravitreal extension.[36] In severely affected capillaries, both pericytes and capillary endothelial cells showed pyknosis, striking vacuolization, and loss of organelles as demonstrated with electron microscopy.[8,36] In advanced retinopathy, degeneration of the choriocapillaris lamina becomes evident,[8] and choroidal neovascular growth may ensue.[36]

Clinical Manifestations

The ophthalmoscopic manifestations of radiation retinopathy are frequently likened to the retinal vascular abnormalities of diabetic retinopathy.[4,8,11] Microaneurysms appear first, followed by retinal hemorrhages, capillary nonperfusion, and infarcts of the nerve fiber layer (Figure 1).[2-4,6,8,9] Retinal edema, hard exudates, telangiectasia, and vascular sheathing may follow in variable sequence and latency.[2-6,9-12] Neovascularization may develop later (Figure 2),[4-7,9,10] with subsequent vitreous hemorrhage and traction retinal detachment,[5,9,10,15] clinically similar to the fibrovascular proliferation seen in diabetic retinopathy. A feature of radiation retinopathy that distinguishes it from diabetic retinopathy is the atrophy of the retinal pigment epithelium seen sometimes after radiation treatment (Figure 3).* Vascular obliteration also gives rise to radiation optic neuropathy, which may manifest as papillitis and optic atrophy (Figure 4).[2,5,12,19,40,41] The latency period between radiation exposure and the clinical manifestation of vascular changes varies, ranging from three weeks to seven years,[6] but most typically is six months to three years.[4,6,9,11,12,31]

The retinopathic changes following radiation exposure are more severe in the posterior than in the anterior retina, and this difference is purportedly due to the increased number of capillaries and higher blood flow of the macular region.[4,12,19] Macular changes may include hard exudates,[11,14] cystoid and noncystoid macular edema (Figure 5),[4,5,9,14] and serous detachment.[11] As would be expected, macular abnormalities frequently lead to a significant loss of vision.

Treatment

Although considerable attention has been focused on the pathogenesis, clinical presentation, and prevention of radiation retinopathy, few articles address treatment. Chaudhuri and co-workers detail therapeutic success using argon laser panretinal photocoagulation in patients with proliferative retinopathy and vitreous hemorrhage.[10] Fluorescein angiography two weeks after treatment showed complete regression of peripheral and optic disc neovascularization. In 1984 Kinyoun and colleagues reported the use of argon laser panretinal photocoagulation in both eyes of a man with neovascularization and vitreous hemorrhage[9]; active fibrovascular proliferation became inactive following treatment. Subsequently, Kinyoun and associates reported the successful treatment of radiation-induced macular edema[38]; leaking microaneurysms were treated with focal photocoagulation and areas of capillary nonperfusion with limited-scatter argon laser photocoagulation. Three of six patients treated with panretinal photocoagulation for proliferative radiation retinopathy showed the regression of new vessels. Similarly, Amoaku and Archer reported a favorable treatment response after focal argon laser photocoagulation in two patients with radiation-induced macular edema.[37] These initial uncontrolled studies indicate that some cases of proliferative radiation retinopathy and macular edema respond favorably to photocoagulation treatment, the goal of which is to decrease vision loss. With respect to the treatment of radiation optic neuropathy, the use of hyperbaric oxygen within two weeks of the loss of vision has proved efficacious in some patients.[42]

Research Issues

Experimentally induced radiation retinopathy is an interesting model for the study of retinal ischemia and proliferative retinopathy. Further research of the biochemical and histologic changes of radiation retinopathy may provide useful information regarding pathophysiology and the rationale for the treatment of ischemic and proliferative retinopathies, regardless of the cause. Irvine and co-workers, using a 4 Mev linear accelerator to irradiate the eyes of capuchin monkeys (*Cebus capucinus*), have proposed that vaso-occlusive retinopathy occurs after a latency period of 12 to 24 months.[8,36] The early retinal vascular abnormalities may progress to intraretinal proliferative retinopathy,[36] with apparent release of a vasoproliferative factor leading to rubeosis iridis. Consequently, vitreous assays may be feasible to monitor biochemical changes after lensectomy and vitrectomy and the

*References 4, 8, 11, 12, 15, 18, 19, 27, 28, 30, 31.

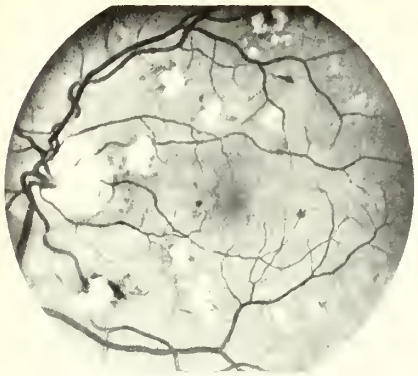

Figure 1.—Fundus photographs of left eye show extensive infarcts of the nerve fiber layer, retinal hemorrhages, and microaneurysms.

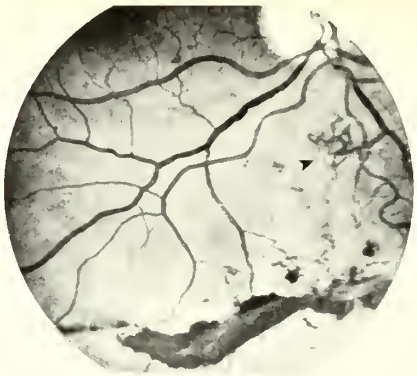

Figure 2.—Retinal neovascular proliferation is shown **(arrowhead)**, with associated hemorrhage.

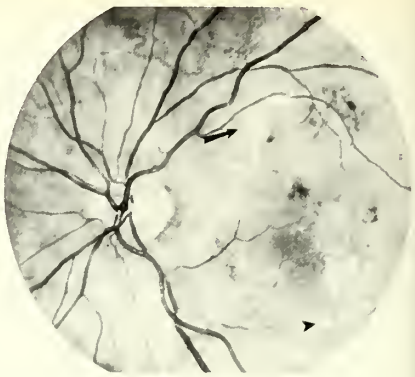

Figure 3.—In radiation retinopathy, atrophy of the macular retinal pigment epithelium occurs **(arrowhead)** in addition to retinal hemorrhages and hard exudates **(arrow)**.

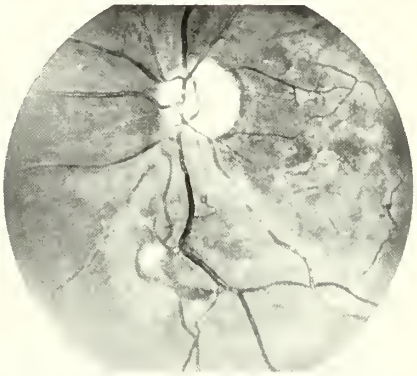

Figure 4.—The eye shows optic atrophy, vascular sheathing, and fibrovascular proliferation.

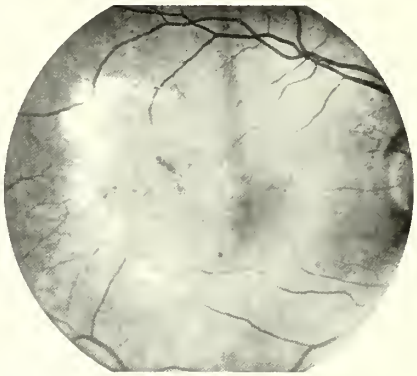

Figure 5.—The macula retinae shows edema with an incomplete ring of hard exudates.

relationship of those changes to the development of rubeosis iridis. An important goal of such research is the development and use of vasoproliferative inhibitors in human disease, such as diabetes mellitus. This model also allows repeated, long-term ophthalmoscopic observations of retinal ischemia as well as easily retrievable pathologic specimens for correlating fluorescein angiography with light and electron microscopy.

Conclusion

Because radiation is being used with increasing frequency for the treatment of ocular and periorbital diseases, it is reasonable to expect that radiation retinopathy may become a more frequently encountered treatment complication despite refinements of dosage calculation and the delivery of the radiation. Consequently, vision loss from radiation retinopathy also may become more common, highlighting the need for new treatments to retard or prevent sight-threatening radiation retinopathy. Photocoagulation is only an initial step in this effort. Although it may be impossible to eliminate the risk of radiation retinopathy, the vision-threatening sequelae can be reduced by good management of these patients. Health care professionals should know the factors that may potentiate the retinopathic effects of radiation, including increased radiation dosage, increased fraction size, concomitant systemic vascular disease, and the concurrent administration of chemotherapeutic agents. These potentiating factors should be minimized. Furthermore, physicians should inform patients about risks and assure ophthalmologic follow-up as indicated.

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* * *

THE OLD ONE AND THE FISH

Laced to her wheelchair,
she watches a fish in a tank
drift through bands of light.
A nurse with tea and cakes
points to a cracker she can have.
With hooded eyes, the old one glares
at the nurse, lifts an elbow
stiff as a shield, and takes a brownie
rich in butter, chocolate chips and nuts.
The eye of the fish, black as death,
tilts to her, diamonds on veined hands,
silk knotted at her throat. In a froth
of gauzy fins the fish rips up
a blade of grass, spits a burst
of salt and pepper sand,
and rams the glass.
"Do it!" the old one says. "Do it again!"

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Charlotte, North Carolina

Articles

Effects of the Multiple Risk Factor Intervention Trial Smoking Cessation Program on Pulmonary Function

A Randomized Controlled Trial

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To determine whether the decline in pulmonary function in smokers is modified by stop-smoking intervention, a randomized controlled study (the Multiple Risk Factor Intervention Trial) was done comparing participants in a special intervention group that included an intensive smoking cessation program with those assigned to usual care. The subjects were 6,347 middle-aged male smokers who had serial measurements of pulmonary function—principally the forced expiratory volume in 1 second (FEV_1)—during 6 to 7 years of follow-up. No overall differences were detected in the rate of loss of FEV_1 in the two groups. The use of β-blockers, which had detrimental effects on FEV_1, was significantly more common in the intervention group. Among nonusers of β-blockers, heavy smokers lost FEV_1 at a rate about 11 ml per year slower in the intervention group than in the control group ($2P=.09$) and ended the trial with an FEV_1 about 90 ml higher ($2P=.05$). These results support the inference from observational studies that smoking cessation has a beneficial effect on pulmonary function in heavy smokers.

(Browner WS, DuChene AG, Hulley SB: Effects of the Multiple Risk Factor Intervention Trial smoking cessation program on pulmonary function—A randomized controlled trial. West J Med 1992 Nov; 157:534-538)

A man who smokes is about ten times more likely than a nonsmoker to die of chronic obstructive pulmonary disease (COPD). In the United States, mortality from COPD due to cigarette smoking is about 14,000 annually and costs about $500 million a year in lost productivity.[1] Although it seems clear that COPD can be largely prevented by a lifelong avoidance of smoking, whether programs that encourage current smokers to quit will have a similar benefit is unknown.

Smokers lose pulmonary function more rapidly than nonsmokers: on the average, the gradual age-related loss of pulmonary function (expressed as the forced expiratory volume in one second [FEV_1]) occurs about 25% to 50% faster in smokers than in nonsmokers.[2-5] Many studies have also shown that cigarette smokers who quit have a slower rate of loss of the FEV_1 than continuing smokers,[2,5-11] especially if quitting takes place before the start of pulmonary dysfunction.[12]

But quitters may differ in several ways from nonquitters; they smoke fewer cigarettes, for example,[13,14] and are less likely to inhale.[13] Confounding factors of this sort, if they are known and have been measured, can be adjusted for when assessing the effects of smoking cessation in an observational study. Only a randomized trial, however, can definitively demonstrate that quitting smoking per se, rather than some unknown or unmeasured characteristic of the quitter, is beneficial in preventing smoking-induced loss of pulmonary function. Randomized trials are not easy to design for this research question: smokers cannot be randomly assigned to quit (or not to quit) smoking, they can only be randomly assigned to receive (or not to receive) an intervention designed to encourage them to quit.

A previous randomized trial of a quit-smoking program reported a statistically significant benefit on pulmonary function in the first year of the study but not in subsequent years.[13] That study assigned 1,445 middle-aged male smokers to either an intervention group that received a series of stop-smoking visits with a study physician or a "normal care" control group. Smokers randomly assigned to the intervention lost an average of 75 ml of FEV_1 in the first year of the study, compared with an average loss of 115 ml in those assigned to the control group. In the next two years of the study, however, the loss of the FEV_1 was actually slightly greater (an additional 56 ml) in the intervention group than in the control group (37 ml). Although the net effect at three years was still reported to be in favor of the intervention, only 61% of those originally randomly assigned to one of the groups had their pulmonary function measured at that time; no further measurements of pulmonary function were made during the remaining seven years of the study.

The Multiple Risk Factor Intervention Trial (MRFIT), though primarily a study of the prevention of coronary heart disease, provided another opportunity to address this question in a randomized trial.[14] About two thirds of the men who volunteered for the MRFIT were cigarette smokers at baseline, and serial measurements of pulmonary function were made during the trial. Technically acceptable pulmonary function measurements were available for 6,347 smokers and were analyzed to determine whether random assignment to

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At the time this work was under investigation and the article being prepared for publication, Dr Browner was an employee of the US government. The article fits the description in the US Copyright Act of 1976 of a "US government work," and therefore there is no copyright.

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ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1 second
MRFIT = Multiple Risk Factor Intervention Trial

the MRFIT smoking-cessation intervention modified the rate of change in pulmonary function.

Subjects and Methods

Subjects and Design

The MRFIT enrolled 12,866 men aged 35 to 57 who were at high risk for coronary heart disease because of elevated blood pressures, serum cholesterol levels, or cigarette smoking.[14] All expressed interest in modifying their cardiovascular risk factors. Men with chronic obstructive pulmonary disease (as diagnosed by the MRFIT examining physician) were excluded.

Half of the men (6,428) were randomly assigned to a special intervention group; the others (6,438) were assigned to usual care and served as the comparison group. The special intervention group participated in an intensive integrated program to lower the three major cardiovascular risk factors (smoking, hypertension, and hypercholesterolemia), and the usual care group received no specific therapy. The smoking cessation intervention has been described elsewhere.[15] The program began with a series of weekly group discussions and continued throughout the trial with counseling and various behavior modification techniques. Subjects were examined annually for six to eight years.

At the start of the trial (screen 3), 3,786 men in the special intervention group (59%) and 3,772 men in the usual care group (59%) were cigarette smokers. Baseline smoking and technically acceptable (described later) pulmonary function data over the period of follow-up were available for 6,347 (84%) of these smokers (3,189 in special intervention and 3,158 in usual care); they comprise the sample for this study. There were no substantial differences in baseline characteristics between those men for whom data were available and the remainder of the study participants.[5]

Measurements

Data were collected by questionnaire for age, race, age at start of cigarette smoking, current number of cigarettes smoked per day (at first screening visit), and medication use throughout the trial, including the use of β-blockers (primarily for the treatment of hypertension). Subjects who reported smoking cigarettes at screening visits 1 and 3 were classified as smokers. Smoking cessation was ascertained by questionnaire and verified by serum thiocyanate levels, an objective measurement of recent smoking.[16]

Pulmonary function, measured by the FEV_1, was determined annually using 10-liter Stead Wells water-filled spirometers. All spirograms were reviewed and rated for several indices of technical quality.[17] Because the measurement of pulmonary function during the first few years of the trial was poorly standardized and of uncertain validity, this report is limited to smokers who had at least three acceptable annual FEV_1 measurements, or two FEV_1 measurements at least two years apart, made after the MRFIT pulmonary function testing was standardized during the third annual visit cycle. A final FEV_1 was defined as an acceptable measurement recorded at the sixth annual visit and was available for 5,634 participants. We were unable to determine directly the effect of the intervention during the early years of the trial. Random assignment, however, of the large number of smokers in MRFIT makes it highly probable that the missing initial FEV_1 values in the special intervention and usual care groups were nearly identical. Any unmeasured benefit of the intervention in preserving pulmonary function in the early years of the trial should be reflected in higher final FEV_1 values in the special intervention group; we were able to measure these last values.

Analysis

The change in the FEV_1 over time was assessed for each participant by calculating the slope of the least-squares regression line of FEV_1 versus time, using three to five measurements of FEV_1 over two to four years of follow-up. Each participant's "slope" was treated statistically as a single observation. Using the method of Fletcher and co-workers, each subject's FEV_1 values were checked for outliers before a slope was calculated.[3(pp179-180)] The FEV_1 at the midpoint of follow-up was estimated by the mean value of all FEV_1s measured. Expected FEV_1 values before and after that time were estimated by assuming an annual decline in the FEV_1 of 50 ml per year, approximately that observed for the entire MRFIT cohort; values that differed by more than 500 ml from the expected value were labeled as outliers. The few subjects with outliers (46 in special intervention, 54 in usual care) were excluded from this report; other analyses that included them produced nearly identical results.

All statistical analyses were done comparing the special intervention and usual care groups using an intention-to-treat analysis without regard to an individual subject's success at stopping smoking. Continuous data are reported as the mean plus or minus one standard deviation. Mean slopes and final FEV_1 values were compared with the t test, and proportions were compared with the z statistic.[18] Nominal two-sided P values are reported, unadjusted for multiple hypothesis testing. Because of the overwhelming prior probability, based on observational studies, that quitting smoking would reduce rather than increase the rate of loss of pulmonary function, two-sided P values of less than .10 favoring special intervention (equivalent to one-sided values of less than .05) were taken as evidence for the inference that the effect observed in our sample is present in the population.[19] Standard techniques were used to determine 90% confidence intervals.[20]

To check the adequacy of randomization, given that some pulmonary function data were missing, we compared baseline characteristics that might be related to pulmonary function—including age, race (percentage of nonwhite), height, and smoking history (cigarettes per day, total pack-years)—in the special intervention and usual care analysis groups. There were no between-group differences in these characteristics among the subjects in the main analysis group, among the nonusers of β-blockers within that group, or among the heavy smokers within that subgroup (all $P > .17$).

Results

At the sixth annual visit, thiocyanate-adjusted quit rates were higher among smokers in the special intervention group (33%) than in the usual care group (20%) ($P < .0001$). In addition, 13% of the smokers in special intervention but only 3% of those in usual care refrained from smoking throughout

the trial ($P < .0001$). There were no significant differences, however, between the special intervention and the usual care smokers in either the rate of loss of the FEV_1 over the final half of the trial or the final FEV_1 value (Table 1). Both groups lost about 60 ml in their FEV_1 per year.

During the trial, study physicians caring for subjects in the special intervention group prescribed β-blockers for the treatment of hypertension more commonly than did the community physicians caring for the subjects receiving usual care. Thus, slightly more smokers in the special intervention group reported the use of β-blockers than did those in the usual care group (22.5% versus 19.8%, $P < .01$). The mean rate of loss of the FEV_1 was about a third higher and the mean final FEV_1 about 100 ml lower in users of β-blockers compared with nonusers (75 ± 114 ml per year versus 56 ± 102 ml per year, $P < .0001$; 2,950 ± 673 ml versus 3,055 ± 685 ml, $P < .0001$). Thus, β-blocker use confounded the effect of the smoking cessation intervention. Stratifying by the use of β-blockers, however, did not reveal any overall differences in pulmonary function between the special intervention and the usual care groups (Table 2).

Further stratification of nonusers by age, total pack-years, and baseline smoking (Tables 3 and 4) shows that the rates of loss of the FEV_1 were higher and the final FEV_1 lower with increasing age, baseline smoking, and total pack-years consumed (Tables 3 and 4). These effects are best

TABLE 1.—*Change in Forced Expiratory Volume in 1 Second (FEV_1) and Final FEV_1 in Smokers in Special Intervention and Usual Care Groups in the Multiple Risk Factor Intervention Trial*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Change in FEV_1, ml/yr	3,189	−60.9	107.0	3,158	−59.6	102.8	−1.3	.62	−5.6, 3.0
Final FEV_1, ml	2,812	3,043	677	2,822	3,022	688	22	.24	−8, 52

TABLE 2.—*Change in Forced Expiratory Volume in 1 Second (FEV_1) and Final FEV_1 in Smokers in Special Intervention and Usual Care Groups in the Multiple Risk Factor Intervention Trial, Stratified by Use of β-Blockers*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Users of β-Blocker									
Change in FEV_1, ml/yr	717	−76.7	115.3	625	−73.4	114.3	−3.3	.60	−13.6, 7.1
Final FEV_1, ml	644	2,950	664	556	2,949	684	1	.99	−63, 65
Nonusers of β-Blocker									
Change in FEV_1, ml/yr	2,472	−56.3	104.0	2,533	−56.2	99.5	−0.1	.97	−4.9, 4.6
Final FEV_1, ml	2,168	3,071	680	2,266	3,039	688	32	.12	−2, 65

TABLE 3.—*Change in Forced Expiratory Volume in 1 Second (FEV_1) (ml/yr) in Smokers in Special Intervention and Usual Care Groups Who Did Not Use β-Blockers, by Age at Entry, Pack-years of Cigarette Smoking, and Baseline Number of Cigarettes Smoked per Day*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Age, years									
35-39	452	−49.0	96.3	494	−50.4	112.6	1.4	.84	−9.9, 12.6
40-44	603	−58.8	114.5	610	−53.1	93.7	−5.8	.34	−15.6, 4.1
45-49	719	−55.5	97.8	690	−59.4	97.7	3.8	.46	−4.7, 12.4
50-54	515	−56.9	105.7	545	−57.6	91.8	0.6	.92	−9.3, 10.6
55+	183	−66.9	105.2	194	−65.0	109.2	−1.9	.87	−20.1, 16.3
Cigarette Smoking, pack-years (Approximate Quartiles)									
0-32	639	−50.9	104.4	615	−49.6	114.6	−1.3	.83	−11.5, 8.8
33-47	608	−56.5	102.2	621	−52.1	95.4	−4.4	.44	−13.6, 4.9
48-64	597	−62.8	99.2	629	−55.8	87.0	−7.0	.19	−15.7, 1.8
65+	628	−55.4	109.7	668	−66.3	99.0	10.9	.06*	1.4, 20.5
Cigarettes/Day (Screen 1)									
1-20	644	−51.8	102.5	628	−49.2	104.2	−2.6	.66	−12.1, 7.0
21-30	599	−62.1	105.0	623	−56.4	88.7	−5.7	.31	−14.8, 3.5
31-40	689	−59.1	99.8	732	−57.3	103.6	−1.8	.74	−10.7, 7.1
41+	540	−51.6	109.7	550	−62.3	100.0	10.7	.09*	0.2, 21.1
Total	2,472	−56.3	104.0	2,533	−56.2	99.6	−0.1	.97	−4.9, 4.6

*Significant at 2-sided $P < .10$ favoring special intervention

TABLE 4.—*Final Forced Expiratory Volume in 1 Second (FEV_1) (ml) in Smokers in Special Intervention and Usual Care Groups Who Did Not Use β-Blockers, by Age at Entry, Pack-years of Cigarette Smoking, and Baseline Number of Cigarettes Smoked per Day*

	Special Intervention (SI)			Usual Care (UC)			SI-UC Difference		
Pulmonary Function	Subjects, No.	Mean	SD	Subjects, No.	Mean	SD	Mean	P	90% Confidence Interval
Age, years									
35-39	389	3,522	613	428	3,421	628	101	.02*	29, 172
40-44	523	3,209	636	540	3,211	643	−2	.96	−66, 62
45-49	640	2,995	616	625	3,001	637	−6	.86	−64, 51
50-54	465	2,785	628	493	2,751	603	34	.39	−30, 100
55+	151	2,621	612	180	2,530	687	91	.21	−27, 210
Cigarette Smoking, pack-years (Approximate Quartiles)									
0-32	557	3,268	692	545	3,300	628	−31	.42	−97, 33
33-47	530	3,133	652	556	3,099	642	34	.39	−30, 98
48-64	536	3,003	658	557	2,984	698	18	.66	−49, 85
65+	545	2,873	651	608	2,799	686	74	.06*	9, 139
Cigarettes/Day (Screen 1)									
1-20	566	3,104	681	556	3,122	658	−18	.64	−84, 47
21-30	529	3,081	713	563	3,058	669	23	.58	−45, 92
31-40	605	3,047	654	656	3,011	698	35	.35	−27, 98
41+	468	3,048	671	491	2,959	724	89	.05*	14, 163
Total	2,168	3,070	679	2,266	3,039	689	31	.13	−2, 65

*Significant at 2-sided $P<.10$ favoring special intervention.

seen in the usual care group: smokers with at least a 65 pack-year history, for example, lost FEV_1 at a rate that was 19% faster than in all other smokers (66.3 ± 99.0 ml per year versus 55.5 ± 99.6 ml per year, $P < .02$) and had a final FEV_1 that was 327 ml lower ($2,799 \pm 686$ versus $3,127 \pm 657$, $P < .0001$).

This stratification also demonstrates statistically significant benefits from the intervention among heavy smokers, whether heavy smoking is defined as at least 65 pack-years of smoking history or as smoking more than two packs of cigarettes per day at baseline. Heavy smokers assigned to the special intervention group lost FEV_1 at a mean rate that was about 16% slower than those in the usual care group. The estimated difference between the special intervention and the usual care groups in the mean FEV_1 slope of 11 ml per year was consistent with the observation that the mean FEV_1 was about 70 to 90 ml greater in the special intervention group at the six-year point in the trial.

The number of users of β-blockers was small; thus, the power to detect any intergroup differences among them was limited. Stratification by age, pack-years, and baseline cigarette consumption showed no intergroup differences for either the FEV_1 slope (all $P > .17$) or the final FEV_1 (all $P > .23$) in those subgroups.

Discussion

Our results suggest that the intervention in the MRFIT—the largest randomized trial of a smoking cessation program ever undertaken—had a beneficial effect on pulmonary function. Among heavy smokers who did not use β-blockers, those who were randomly assigned to the special intervention group had a 16% slower rate of loss of FEV_1 over the latter half of the trial than the controls receiving usual care. They also had a significantly greater FEV_1 at the end of the trial. Because many smokers in the special intervention group continued to smoke (and some smokers in the control group quit), our results actually underestimate the beneficial effect on pulmonary function of quitting.

These findings are consistent with the overwhelming evidence from nonrandomized studies showing that smokers have a more rapid loss of the FEV_1 than nonsmokers and that quitting smoking slows that decline. We observed this within the MRFIT itself, at least during the latter half of the trial when pulmonary function data were available. Continuing smokers lost FEV_1 at a rate of 60.4 ml per year, compared with 51.9 ml per year in those who quit.[5] These results are consistent with recent estimates by Tager and associates that middle-aged male smokers lose FEV_1 at a rate about 10 ml per year faster than nonsmokers.[21] Other investigators have shown the harmful effects of smoking and the beneficial effects of quitting on other measures of pulmonary function, including expiratory flow rates,[8,11,12,22,23] the ratio of the closing volume to vital capacity,[6,12,22] and the slope of phase III of the single-breath nitrogen washout.[6,7,10] We cannot determine whether using one of these more sophisticated tests would have enabled us to detect an overall intervention effect.

There was no effect of the intervention on pulmonary function among the entire MRFIT cohort of smokers, among those who used β-blockers, or among light smokers. Likely explanations for these results are that most smokers in the special intervention group continued to smoke, whereas some smokers in the usual care group quit; compared with the effect of β-blocker use, the effect of quitting smoking on pulmonary function is small[24-26]; compared with the intrinsic variability in measurements of FEV_1 and the age-related declines in pulmonary function, the effect of quitting in light smokers is modest; and the overall effect was dominated by the light smokers, who made up the majority of our sample. Only after excluding users of β-blockers and then only among heavy smokers, who had a substantially greater loss of pulmonary function, were the effects of the intervention

manifest. In light smokers, for example, the standard deviation of the annual change in FEV_1 of about 100 ml per year was 13 times greater than the projected benefit of 8 ml per year (assuming the same 16% reduction in FEV_1 slope that was observed among heavy smokers). As the confidence intervals in Tables 3 and 4 indicate, our study did not have adequate power to exclude the possibility of a small benefit in these lighter smokers.

This study is subject to several potential biases. The MRFIT was not primarily designed to study pulmonary function: acceptable data were available for only 84% of the subjects, raising the possibility of selection bias. This seems unlikely, however. There were no substantial intergroup differences either in the baseline characteristics known to affect pulmonary function—including age, race, height, and smoking history—or in the frequency of technically unacceptable measurements of FEV_1.

As to co-intervention bias, it is possible that some other aspect of the multifactorial intervention used in the trial was responsible for the observed differences in pulmonary function. There is no reason to think that dietary counseling to reduce elevated serum cholesterol levels would have such an effect, but β-blockers (which reduce the FEV_1) were used to treat hypertension more often in men in special intervention than in those in usual care. This has been dealt with in the analysis by stratification—looking just at the nonusers of β-blockers in both groups—but adjusting for a postrandomization factor in this way does not entirely eliminate the possibility of confounding. It remains possible, for example, that physicians providing special interventions were more likely than those providing usual care to prescribe β-blockers in heavy smokers who were destined for other reasons to be rapid losers of pulmonary function. The remaining heavy smokers in special intervention who did not use β-blockers would then have slower rates of loss of pulmonary function than those receiving usual care, which would falsely appear to be an effect of the intervention. Given that the detrimental effects of β-blockers on pulmonary function were well known to clinicians years before the start of the trial[24] and that the baseline characteristics of heavy smoking nonusers of β-blockers were similar in both groups, confounding of this sort seems unlikely.

The results in the heavy smokers might represent a type I error—finding an effect by chance in the MRFIT sample, or in a subgroup of that sample, that would not be present in the population. We think, for example, that chance is the most likely explanation for the apparent benefit of the intervention on the final FEV_1 but not on the rate of loss of FEV_1 in 35- to 39-year-old men. Our results in heavy smokers have internal consistency, however. We found a substantial positive effect on two separate albeit not entirely independent measures of pulmonary function (change in FEV_1 and the final FEV_1) and using two definitions of heavy smoking—baseline consumption of more than two packs per day and the highest quartile of pack-years of smoking history. Although we tested several hypotheses, we did not dredge the data for significant P values: both outcome variables (annual change in FEV_1 and final FEV_1) and all five predictor variables (special intervention versus usual care, use of β-blockers, age, pack-years, and baseline cigarette consumption) were selected a priori; these were the only variables examined. Similarly, the decision to use a two-sided α of .10 for pulmonary function comparisons favoring the special intervention group was made before we analyzed the data. When the P values we report are viewed in the context of the prior probabilities of the tested hypotheses[19]—in this case the wealth of observational evidence that has shown quitting smoking to be associated with a slower rate of loss of pulmonary function—it seems unlikely that the results in heavy smokers are due to chance. Still, subgroup analyses must be viewed with caution; a conservative interpretation is that our results suggest, but do not establish, that there is a benefit in heavy smokers.

In conclusion, we have found that randomly assigning heavy smokers to a smoking cessation program slows the rate of loss of pulmonary function by about 16%—a beneficial effect of more than 10 ml per year in the FEV_1. We think that this benefit is real and that it can be indirectly generalized to lighter smokers and probably to women. It will be difficult, however, to demonstrate such a benefit using a randomized design. Most important, our results suggest that even among heavy and long-term smokers, it is not too late to quit.

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Articles

Medications in Older Patients

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Adverse drug reactions are common in persons aged 65 and older and are associated with increased morbidity and mortality. A heightened susceptibility to adverse reactions is due to a number of factors, including an increased incidence of disease, multiple drug use, and altered pharmacokinetic and pharmacodynamic properties of many drugs. The risk of drug interactions increases with the number of medications taken. Adverse drug reactions can be prevented through prudent prescribing practices, patient education, and adequate monitoring of drug efficacy and side effects. Several types of medications are of particular concern, including many antihypertensive agents, drugs with anticholinergic effects, psychoactive medications, and nonsteroidal anti-inflammatory drugs. Some drugs, such as histamine H_2-receptor antagonists, are relatively safe but are overprescribed. Data regarding the risks associated with these problem drugs are presented, with recommendations for safe and effective treatment alternatives.

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The proper use of medications in older persons is an important topic for primary care physicians, medical specialists, and surgeons. In the United States, older patients are major consumers of pharmaceuticals, using 40% of all prescription medications. In this article I review factors that influence the efficacy and safety of medications in older persons, examine particular problem drugs, and suggest practical guidelines for drug prescribing.

Although the appropriate use of medications can prevent, control, or cure disease, inappropriate use may have serious consequences. Because of changes in homeostatic mechanisms and supervening diseases, elderly persons are less tolerant of many drugs. About 10% to 30% of geriatric hospital admissions are due to medication toxicity,[1,2] and 1 of 1,000 older patients admitted to a hospital dies of an adverse drug reaction.[3] The risk of adverse drug reactions is probably related more to the degree of frailty and medical condition of the patient, however, than to age alone.[4]

Older patients are different from younger ones in several ways that may affect safe medication use. Older persons have an average of five coexisting medical conditions, and the treatment of one problem may adversely affect another. Also, they are especially prone to polypharmacy: the average older person takes 4.5 medications and fills 13 prescriptions yearly.[5] Because of cognitive, functional, and social factors, some older persons differ from their younger counterparts in their ability to comply with medication regimens.

There is a deficit of information about the efficacy and safety of drugs in elderly persons. Most drug trials exclude the old and infirm, and it is not until after Food and Drug Administration approval and widespread use that the actual incidence and severity of toxicity are known.

Pharmacokinetics

Pharmacokinetics refers to the temporal absorption, distribution, metabolism, and excretion of a drug. Because of physiologic changes, disease states, and other medications, the pharmacokinetics of many drugs are altered in older persons (Table 1).[6]

Except in special cases, changes in the absorption of medications are of little clinical consequence. Decreased gastric acid production may decrease the absorption of cations such as iron and calcium, and medications that increase the gastric pH will accentuate this physiologic change. Decreased gastrointestinal motility and splanchnic blood flow may slow absorption and delay the onset of action of a drug but do not usually alter the total amount of drug absorbed.

Well-documented changes in the body composition of most older persons affect the volume of distribution of a drug, depending on its fat or water solubility. Because of a relatively smaller lean body mass, most older persons require a smaller loading dose of water-soluble drugs like digoxin. Conversely, because of older persons' expanded fat stores, fat-soluble drugs such as benzodiazepines distribute

TABLE 1.—*Physialagic Changes in Older Persans and the Effect an Selected Drugs*

Physiologic Alterotion	*Effect on Drugs*	*Exomples*
Decreased gastric acid	Reduced absorption of cations	Iron, calcium
Decreased lean body mass	Increased levels of water-soluble drugs	Digoxin
Increased fat stores	Increased half-life of fat-soluble drugs	Benzodiazepines
Diminished serum albumin level	Increased activity of highly bound drugs	Phenytoin
Reduced hepatic oxidative metabolism	Increased drug concentrations	Theophylline
Reduced hepatic blood flow	Decreased first-pass metabolism	Lidocaine, isosorbide
Decline in renal function	Reduced renal clearance	Aminoglycosides, digoxin, ciprofloxacin

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to a larger compartment, from which they are more slowly cleared. In addition, because serum albumin levels tend to decrease with age, drugs that are substantially bound to albumin have a higher concentration of free, active drug at any given serum level. For example, target levels of phenytoin need to be adjusted downward in proportion to a decrease in albumin levels.

Altered metabolism and excretion of drugs are, by far, the most clinically important changes that occur with aging. In the liver, a reduction in the activity of the cytochrome P-450, or oxidative pathway, may reduce the clearance of drugs such as theophylline that are metabolized in this manner. Other processes such as glucuronidation are relatively unaffected. In addition, elderly persons tend to have a lower resting cardiac output, which reduces hepatic blood flow. Therefore, drugs such as isosorbide and lidocaine that are flow dependent in their hepatic metabolism should be started at lower doses and titrated according to clinical effect or blood level.

Most older persons have a decreased ability to excrete medications in the urine. Cross-sectional studies have shown a linear decline of 50% in renal function by age 85. Longitudinal studies, however, reveal considerable individual variation.[7] Long-standing diabetes mellitus, hypertension, or other risk factors increase the likelihood of notable impairment. Unfortunately, the serum creatinine level may be an unreliable indicator of renal function. The Cockcroft-Gault equation* is a useful tool to estimate creatinine clearance from the serum creatinine level, taking into account the patient's age, weight, and sex.[8] The value derived from this equation may be unreliable if renal function is changing rapidly. When using potentially toxic drugs with primarily renal excretion, such as digoxin, it is important to use measured drug levels, when available, to ensure safe dosing. Many other commonly prescribed drugs are cleared by the kidneys. These include the combination of sulfamethoxazole and trimethoprim, ciprofloxacin, and H_2-receptor antagonists. Generally if the estimated creatinine clearance is less than 30 ml per minute, the dose of such drugs should be halved. If the estimated creatinine clearance is less than 15 ml per minute, a timed urine collection and consultation with a clinical pharmacologist are recommended.

Pharmacodynamics

Pharmacodynamics can be defined as the body's sensitivity to medications. Many pharmacodynamic changes must be considered when prescribing medications in elderly persons.[9] In general, older persons are more sensitive to the central nervous system (CNS) effects of most drugs, particularly if there is underlying cognitive impairment. It has been shown that many medications, including sedatives, antihypertensives, analgesics, and H_2-receptor antagonists, are associated with cognitive impairment.[10] Benzodiazepines cause more psychomotor impairment in older than in younger persons, not accounted for by differences in blood levels.[11] In the elderly, narcotics not only have increased CNS effects, but these effects may be qualitatively different—delirium instead of oversedation.[12] Increased CNS effects from anticholinergic agents are probably due to an age-related decline in cholinergic activity in the brain.

The anticoagulant effect of warfarin sodium may be enhanced in older persons; elderly patients generally require a lower dose.[13] In addition, they are more likely to bleed while anticoagulated because of a higher prevalence of predisposing conditions.[14]

There is also convincing evidence that older patients are less responsive to β-blockers. This appears to be due to reduced receptor sensitivity, especially at the β_1-receptor.[15]

Drug Interactions

Patients who take several medications concurrently are at risk for substantial drug interactions[16]; this risk increases with the number of medications. It is estimated that the rate of adverse effects is 4% for persons receiving 5 or fewer drugs, 10% for those receiving 6 to 10 drugs, and 28% for those receiving 11 to 15 drugs.[17] Drugs may interact with each other when they have opposing effects (the renal effects of nonsteroidal anti-inflammatory agents and diuretics), when they have similar effects (sedation from anticholinergic agents and benzodiazepines), or when they alter each other's pharmacokinetics.

Drugs also interact with diseases, causing adverse effects. Examples of this phenomenon are plentiful and include acute urinary retention in persons taking anticholinergic agents and worsened congestive heart failure due to β-blockers.

Drug-nutrient interactions are also common.[18] The absorption of drugs such as levodopa, isoniazid, tetracycline, erythromycin, and oral β-lactamase antibiotics is notably inhibited by the presence of food in the stomach. The absorption of other drugs, including nitrofurantoin and propranolol hydrochloride, is increased by administering with food. There is convincing evidence that the bioavailability of phenytoin suspension is dramatically reduced in patients receiving continuous enteral feedings.[19] Drugs may also cause substantial nutrient depletion. Clinically important interactions of this type include isoniazid-induced vitamin B_6 deficiency and diuretic-induced potassium and magnesium depletion.

To screen for possible drug interactions, a complete list of all medications and medical problems should be kept for every patient. Note that there are several types of drugs that patients may fail to report. These include over-the-counter medications, ophthalmic preparations, topical medications, liquids, and vitamins. If there is any question, the patient should be instructed to bring in all medication bottles, or a home visit should be carried out. Also, patients should be asked about alcohol use; alcohol has the potential to interact with at least half of the most commonly prescribed drugs.[20]

Principles of Prescribing for Older Patients

When prescribing a new medication in an old or frail person, the following principles should be considered:

- Decide if the disease or symptom is worth treating. Some conditions may not require any intervention or may respond adequately to nonpharmacologic approaches. The treatment of many conditions, such as hyperlipidemia,[21] is of unproven benefit in elderly patients.
- Review the risks of treatment and of substantial drug interactions. In some patients an otherwise useful medication is contraindicated because of the risk of adverse effects. In particular, remember to consider the possible effects of a drug on a patient's function and quality of life.
- Assess the patient's ability to comply with the treatment regimen. Common reasons for noncompliance include

*Creatinine clearance = (140 − age) × weight (kg)/serum creatinine (mg per dl) × 72, multiply by 0.85 for women.

an inability to obtain medications—cannot get to the pharmacy or pay for the drug—trouble remembering to take medications, side effects, and difficulties opening a bottle or swallowing pills. Patients living alone may be particularly vulnerable to noncompliance. Intentional noncompliance is common.[22] Patients may alter a dosing regimen to reduce side effects, to acquire greater self-control, or for convenience. For example, it is common for older persons with urinary incontinence to avoid diuretics on days they plan to go out of the home.

Efforts to enhance compliance begin with assessing current medication use. Try to limit the total number of medications, and keep dosing regimens simple, using medications with once- or twice-a-day dosing requirements where possible. Patient and family education is important. Medication delivery aids such as seven-day pillboxes that are filled according to day and time (for example, Mediset boxes) are also helpful.

- Start low and go slow. To avoid untoward effects, it is prudent to begin most medications at a low dose and to increase the dose slowly. This is especially important with antihypertensive and psychoactive drugs where patient sensitivity may be unpredictable and the consequences of overtreatment severe.
- Monitor therapy for efficacy and side effects. When starting a drug regimen, determine how its effects will be monitored and plan an approximate duration of therapy. Medications should be reviewed at each office visit and at every hospital admission and discharge. Many medications may be started or continued unnecessarily and can be safely withdrawn.

Problem Drugs

Problem drugs are those that have a high potential for toxicity and those that are relatively safe but are not efficacious or are overprescribed.

Antihypertensive Drugs

Antihypertensive agents can cause orthostatic hypotension, sedation, depression, impotence, and constipation.[23] In general, elderly persons are less tolerant of central adrenergic inhibitors like clonidine and peripheral α-adrenergic blockers such as prazosin hydrochloride. Low-dose thiazide diuretics are relatively safe for most patients and cause less metabolic aberrations and hypovolemia than higher doses. Calcium channel blockers are theoretically ideal, but nifedipine may cause orthostasis and edema, and diltiazem and verapamil hydrochloride are contraindicated in patients with ventricular systolic dysfunction. Verapamil causes considerable constipation, and the other calcium channel blocking agents do so to a lesser extent. Angiotensin-converting enzyme inhibitors can reduce renal function in predisposed patients or when combined with other drugs such as nonsteroidal anti-inflammatory agents. β-Blockers may have reduced efficacy, more CNS effects, and are contraindicated in many common conditions. Overall, the choice of antihypertensives will depend on a patient's susceptibility to certain side effects and on coexisting conditions. In patients with blood pressure measurements persistently higher than 160/95 mm of mercury and in whom a program of sodium restriction and exercise fails, initial treatment with 12.5 to 25 mg per day of hydrochlorothiazide (or an equivalent) is recommended. If this treatment fails and the patient has normal cardiac function, sustained-release diltiazem, 120 to 480 mg per day in two doses, can be added or substituted. For those with congestive heart failure, a judicious trial of an angiotensin-converting enzyme inhibitor such as lisinopril is indicated. If this is not tolerated due to renal dysfunction or cough, other medications with prominent arterial vasodilatory effects such as nifedipine or hydralazine hydrochloride may be useful.

A difficult subset of patients to treat are those with hypertension and orthostatic hypotension.[24] These patients typically have hypovolemia and become dangerously orthostatic when given diuretics. The using of pindolol, a β-blocker with intrinsic sympathomimetic activity, may improve orthostasis. To reduce supine hypertension, the head of the patient's bed should be raised. In any case, close monitoring of orthostatic symptoms and close follow-up are recommended.

Anticholinergic Drugs

Drugs with anticholinergic effects include antidepressants, antipsychotics, antihistamines, and intestinal and bladder relaxants. Orthostatic hypotension is a common and potentially serious side effect of these agents and can contribute to immobility, falls, and fractures. In addition, anticholinergics may precipitate acute urinary retention in predisposed patients and cause sedation, confusion, and delirium. Less serious but troublesome side effects include dry mouth, blurred vision, and constipation.

Psychoactive Drugs

Though often useful, psychoactive medications must be administered with extreme caution and restraint in older persons. The initial treatment of insomnia, for example, should concentrate on nonpharmacologic approaches and the treatment of symptoms such as pain and nocturia that contribute to sleeplessness. In intermediate and long-term care facilities, attention has been focused on the use of psychoactive medications as "chemical restraints." About half of nursing home patients receive these medications (26% antipsychotics, 28% sedative-hypnotics).[25] This apparent overuse has led to increasing requirements for documenting medical indications and for periodic reviews.

For insomnia, long-acting benzodiazepines such as diazepam and flurazepam hydrochloride may have week-long half-lives in elderly patients, cause daytime sedation and mental slowing, and increase the risk of falls and fractures.[26] Shorter acting agents are much safer, especially if low doses are used intermittently. Lorazepam, 0.5 to 1 mg, is ideal because of its rapid onset of action, and it can also be absorbed from the buccal mucosa for patients who cannot swallow pills. Triazolam is short-acting but can cause more severe rebound insomnia and paradoxic agitation.[27] In addition, peak levels of triazolam are twofold higher in healthy older persons than in younger subjects, resulting in greater psychomotor impairment.[28] Chloral hydrate is a good choice for insomnia because it has less potential for addiction and abuse. Diphenhydramine hydrochloride and amitriptyline hydrochloride should be avoided because of their anticholinergic side effects.

Antipsychotic Drugs

Antipsychotic agents are frequently prescribed for agitation and behavioral problems in patients with dementia. Despite their popularity, there is little information confirming

their efficacy. In a review of the few randomized, controlled clinical trials, improvement over placebo use was modest at best.[29] In addition to questionable efficacy, antipsychotics have substantial side effects. Extrapyramidal movement disorders, including akathisia (motor restlessness), parkinsonism, and tardive dyskinesia, are common and uncomfortable side effects of these drugs. Antipsychotics also have anticholinergic side effects and are associated with a twofold increase in the risk of hip fracture.[26] Improvement in nonpsychotic patients is likely due to sedation. Therefore, when nonpharmacologic approaches fail, it is preferable to achieve sedation with intermittent, shorter-acting benzodiazepines. Lorazepam, 0.5 to 1 mg, may be given three or four times a day when needed. This approach avoids anticholinergic and extrapyramidal side effects and may also palliate underlying anxiety symptoms. Increasing clinical experience suggests that buspirone, a serotonergic anxiolytic with no sedative properties, may also be useful. Neuroleptic agents should be reserved for patients who have prominent delusions, hallucinations, or both and may be tried in patients in whom other pharmacologic approaches have failed. Of the phenothiazines, haloperidol is recommended because it has fewer anticholinergic effects.

Antidepressant Drugs

Antidepressants can be helpful in episodes of major depression. When considering pharmacotherapy, it is important to distinguish major depression from medical disease such as hypothyroidism and less severe dysphoric syndromes. Amitriptyline and doxepin hydrochloride are extremely anticholinergic and sedating, and their use should be avoided. If a sedating agent is needed, trazodone hydrochloride is preferred because it has minimal anticholinergic side effects.[30] For depression with psychomotor slowing, desipramine hydrochloride or nortriptyline hydrochloride are effective and are better tolerated than other tricyclic antidepressants. Fluoxetine may cause anorexia and weight loss, but it has virtually no anticholinergic or sedative effects. The role of psychostimulants such as dextroamphetamine or methylphenidate hydrochloride in geriatric depression is dubious: only one of ten controlled studies showed advantage over placebo.[31]

Hypoglycemic Drugs

The use of hypoglycemic agents must be closely monitored in elderly patients. Hypoglycemic episodes may manifest atypically as confusion or apathy and therefore go undetected. Chlorpropamide has a half-life of several days in patients with renal impairment and is also associated with hyponatremia due to inappropriate antidiuretic hormone excretion. Because of its short half-life, tolbutamide taken with meals is the safest alternative for patients who have an erratic caloric intake. Tolazamide, glyburide, and glipizide can be given once a day to enhance compliance and have similar efficacy and side effects.[32] Tolazamide is available in generic form and is considerably less expensive.

Digoxin

The use of digoxin for congestive heart failure in patients with normal cardiac rhythm has been questioned.[33] Although several studies have shown that digoxin can be safely withdrawn in 50% to 100% of such patients, a subset of patients with ventricular gallops (and presumably poor systolic function) do benefit from its use. Because symptoms of cardiac failure may also be caused by diastolic dysfunction, cardiac ischemia, or primary pulmonary disease, it is vital to verify the presence and degree of systolic dysfunction before prescribing this potentially toxic medication.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory agents are commonly used by elderly persons and are available over the counter. Although these agents improve the quality of life for many patients with arthritis, they must be used with caution. In healthy elderly patients elevated serum creatinine levels rarely develop due to nonsteroidal drug therapy, but patients with renal disease, volume depletion, low cardiac output, or who are taking angiotensin-converting enzyme inhibitors are at higher risk.[34] Dyspepsia develops in at least a third of older persons, gastric or duodenal erosions in 20%, and major complications such as bleeding and ulcer perforation in 1% to 2%.[35] These side effects may be mitigated by the coadministration of antiulcer drugs or misoprostol. Central nervous system side effects of sedation and confusion also occur with nonsteroidal therapy. Acetaminophen, enteric-coated aspirin, and intermittent intra-articular administration of corticosteroids are useful alternatives for patients at risk for serious adverse reactions.[36]

H_2-Receptor Antagonists

Overall, H_2-receptor antagonists are safe and effective therapy for peptic ulcer disease, but they are greatly overused

TABLE 2.—*Recommended Drug Treatment Alternatives for Common Conditions in Elderly Patients*

Condition	*Recommended Drug*	*Use With Caution*
Hypertension		
Without LV failure	Low-dose thiazide diuretic plus or minus slow-release diltiazem HCl	Clonidine and other central adrenergic inhibitors; prazosin HCl
With LV failure	Lisinopril or enalapril maleate; if renal failure, hydralazine HCl	β-Blockers, diltiazem HCl, verapamil HCl
With significant orthostatic hypotension	Pindolol	Diuretics, central adrenergic inhibitors, prazosin HCl, nifedipine
Diabetes mellitus	Tolazamide	Chlorpropamide
Arthritis	Acetaminophen, enteric-coated aspirin, ibuprofen (with monitoring)	Indomethacin, piroxicam
Insomnia	Chloral hydrate, lorazepam*	Diazepam, flurazepam, triazolam, diphenhydramine HCl
Agitation in dementia	Lorazepam*	Phenothiazines
Depression	Trazodone HCl, desipramine HCl	Amitriptyline HCl

HCl = hydrochloride, LV = left ventricular

*With intermittent or as-needed dosing

in patients with nonulcer dyspepsia, patients without recent disease, and as prophylaxis in patients admitted to hospitals. Any H_2 blocker can cause CNS effects, especially at higher doses and in those with renal or hepatic impairment.[37] Cimetidine also has many drug interactions: it substantially inhibits the hepatic metabolism of warfarin, phenytoin, lidocaine, quinidine, and nifedipine, among others, and decreases the renal excretion of procainamide hydrochloride. Recommendations for the drug treatment of common conditions in elderly persons are summarized in Table 2.

Conclusions

Adverse drug reactions are common in elderly patients but often preventable. A knowledge of altered physiologic processes from normal aging and supervening diseases facilitates the selection of appropriate therapy and limits adverse reactions. Awareness of the dangers associated with multiple drug use and with specific medications is important, as is continuous monitoring of patients to determine whether the prescribed drug regimen is beneficial. Understanding a patient's treatment goals, social situation, and functional state, in combination with patient education, may improve medical compliance. Finally, it is paramount to consider the effects of medications on a patient's functional state and quality of life. Preserving functional independence and symptomatic relief are frequently more important than prolonging life in elderly persons, and this "geriatric imperative" should be reflected in medication prescribing, as in all other aspects of care in this challenging population.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Conferences and Reviews

Wake Up and Smell the Coffee

Caffeine, Coffee, and the Medical Consequences

Discussant
TONY CHOU, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER BOUSHEY, MD*: *The recent decline in caffeine and coffee consumption reflects the widespread public awareness of the debate about possible adverse effects of caffeine on health. The enormous popularity of coffee and other caffeine-containing beverages makes this a matter of considerable importance in the field of public health. Caffeine has been implicated in diseases of a number of organ systems, and much concern, in particular, has been raised regarding its possible role as a risk factor in cardiovascular disease and pancreatic cancer. It is therefore a pleasure to introduce at this conference Tony Chou, MD, who will discuss the medical consequences of caffeine. Dr Chou is a native of West Virginia who graduated with honors from the Carnegie-Mellon University (Pittsburgh, Pa) with degrees in electrical engineering and physics. He obtained his MD degree at Case Western Reserve University (Cleveland, Ohio) and completed his residency training in internal medicine at UCSF. As a Medical Chief Resident, Dr Chou has served the numerous constituencies of our department superbly with energy, scholarship, and an enthusiasm for medicine.*

TONY CHOU, MD†: Through the ages, humanity's diligent search for stimulants has been rewarded by the discovery of the coffee bean (*Coffea arabica*) in Arabia, the tea leaf (*Thea* [or *Camellia*] *sinensis*) in China, the kola nut (*Cola nitida* and *Cola aluminata*) in West Africa, the cocoa bean (*Theobroma cacao*) in Mexico, and other plant sources of caffeine.

Caffeine is the most widely consumed stimulant drug in the world, about 75% being taken in the form of coffee. Five million tons of coffee are produced annually in 50 coffee-growing countries. It is second only to oil in international commerce, albeit a distant second. Americans consume about 45 million pounds of caffeine annually with an average daily intake of 200 mg.

More than half of Americans drink coffee daily. An even greater percentage take in caffeine in one form or another each day. The effect of this consumption on health has been the subject of much debate, and public awareness has led to a recent decrease in the amount of caffeine consumed. Caffeine and coffee consumption have been linked to diseases from myocardial infarction to schizophrenia. The studies that have examined the effects of coffee and caffeine on health often discuss the substances interchangeably. An important question is, Is it caffeine or some other substance in coffee that might cause disease?

A Brief History of Coffee

Coffee was first discovered around 850 AD by a goatherder named Khaldi in Abyssinia (Upper Egypt). Legend has it that one night his usually reliable goats did not return home. The following morning he found the animals dancing around a shiny, dark-leaved shrub with red berries. He nibbled some of the berries and, according to the legend, joined in the dance. Thus, the coffee bush was discovered. Khaldi shared his discovery with some local monks who experimented with the berries, tossing them on a fire and then soaking them in boiling water. The liquid turned out to be tasty, and drinking it allowed the monks to stay up through marathon prayer sessions. Thus, the beverage coffee was born and spread, from monastery to monastery, country to country, and continent to continent.

The coffee bean is a seed. The seeds are hulled and dried from berries of coffee tree blossoms. In general, each berry contains two oval beans. The best coffees are picked just as the berries ripen. The outer skin is immediately scraped loose, exposing the bean. There are hundreds of coffee species, but the finest are said to grow from the fragile *C arabica*, which is the principal bean of world-class coffees. Other strains, such as *C arobusta*, are frequently used for "instant" coffees. Freshly picked green beans are roasted, usually in a rotating drum, over a heat source. The end product is the beans that are ground for making coffee or are further processed for other uses.

Instant coffee was first developed at the turn of the century and became popular with the troops in the two world wars and then at home. Two basic techniques are used to produce the instant powder, "spray-drying" and freeze-drying. Instant coffee differs chemically from regular coffee. The "instantization" process conserves about 48% of the solids from the original bean. This is much higher than the 24% solid component conserved by household coffee brewing techniques. Thus, instant coffee has more "coffee."

Caffeine was first removed from coffee in the early 1900s, and decaffeinated coffee became popular in the 1930s with the introduction of Sanka. In most instances, coffee is

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TABLE 1.—*Total Soluble Solids in 225 ml (7.5 fl oz) of Coffee**

Chemical	Caffee: Roasted and Ground (1.544 grams), grams	Caffee: Soluble Spray-Dried (2.318 grams), grams
Caffeine	0.095	0.074
Chlorogenic acid	0.213	0.197
Reducing sugars—sucrose, glucose, mannose	0.168	0.197
Other carbohydrates—inositol, sorbitol, mannitol	0.230	1.008
Peptides—glutamate, glycine, aspartate	0.069	0.278
Potassium	0.115	0.085
Other minerals—calcium, magnesium, copper	0.157	0.104
Acids—quinate, acetate, citrate, maleate	0.199	0.232
Trigonellin	0.059	0.039
Volatiles—sulfur compounds, aldehydes	<0.0001	<0.0001
	1.15	1.99

*Adapted from Clinton.[3]

decaffeinated by removing the caffeine from the beans before roasting. The US Food and Drug Administration allows two organic solvents to be used in the decaffeination process: methylene chloride and ethyl acetate. Methylene chloride, the more common of the two used, has been reported to cause cancer in animals when given in high doses. This has led many companies to try to develop a pure-water process to decaffeinate coffee beans. Such a process has been patented by Nestlē along with other manufacturers. All of Nestlē's varieties of decaffeinated Taster's Choice and Nescafē are water purified.[1]

Chemistry of Coffee

Literally hundreds of chemicals have been identified in coffee (Table 1),[3] and it would be remarkable indeed if caffeine proved to be the only pharmacologically active substance. Chemical substances in coffee include chlorogenic acid, reducing sugars, other carbohydrates, peptides, and potassium. Chlorogenic acid is present in even greater quantities than caffeine.[1,2]

Of interest, there appears to be a compound in instant coffee that binds to the opiate receptor. This compound competes with tritiated naloxone for binding to opiate receptors in rat brain and has been characterized as one of several isomeric (iso)feruloylquinic lactone compounds present in coffee.[4] A cup of instant coffee contains effectively a third of an ampule of naloxone. The importance of these substances on the reinforcing properties of caffeine and coffee intake is not known.

Several mutagens have been reported in coffee. Firm evidence for mutagenicity in humans, however, has been lacking to date. One such mutagen, methylglyoxal, is also found in tomatoes and boiled potatoes. To date, no substance is found in coffee the biologic or chemical properties of which do not occur in other foods.[5]

Caffeine Consumption

In 1983, 80% of the population in the United States drank coffee. This has been on the decrease of late, with the International Coffee Organization reporting in 1991 that only 53% of Americans drank coffee, with an average intake of more than three cups per day. Higher amounts are consumed in Central and South America and Western Europe. The highest consumption occurs in the United Kingdom and Scandinavia, especially Sweden and Finland. The average consumption in these countries is about double that in the United States.

The average US daily consumption of caffeine is about 200 mg. On a milligram-per-kilogram basis, the average consumption of caffeine in the United States and Canada is about 2.4 mg per kg per day for adults and 1.1 mg per kg per day for children 5 to 18 years old. For example, a 27-kg child drinking three colas and eating three small chocolate bars in a day will ingest 7.2 mg per kg of caffeine. Heavy drinkers of caffeinated coffee (in the United States, the top 10% of coffee drinkers) can consume more than 1 gram per day or about 15 mg per kg of caffeine. A caffeine intake of 200 mg per day is equivalent to about two cups of coffee per day. Continuous use at this level over a one-year period would yield "2 cup-years" cumulative caffeine consumption, a unit sometimes used in the literature. A cup-year is equivalent to 16 lb of coffee per person per annum.

Concentrations of caffeine in coffee or tea depend on the particular bean or leaf being used (Table 2).[6] Analysis of the common coffee cup size in homes indicates that the median cup size for coffee or tea is 225 ml or 7.5 oz. In a median cup, drip coffee has the most caffeine content, with 115 to 175 mg per cup. Brewed coffee is the next most potent at 80 to 135 mg per cup. Instant coffee contains 65 to 100 mg, and decaffeinated coffee yields 3 to 4 mg per cup.

TABLE 2.—*Caffeine Content of Coffee and Tea**

Beverage	Caffeine, mg
Coffee (7.5 oz cup or 225 ml)	
Drip	115-175
Brewed	80-135
Instant	65-100
Decaffeinated	3-4
Tea (5 oz cup)	
1-min brew	20
3-min brew	35
Iced (12 oz)	70

*From Bunker and McWilliams.[6]

Tea in general is lower than coffee in caffeine per serving (Table 2). The caffeine content also depends on the brew time. Of the tea varieties, black tea is the most caffeinated, followed by oolong and green teas. A 12-fl oz glass of iced tea contains about 70 mg of caffeine.

Caffeine is added to many sodas (Table 3). Jolt, a recently released beverage, advertises that it contains "twice the sugar" and "twice the caffeine of other colas" and has the highest caffeine content per 12-oz can. Regular Coca-Cola and Diet Coke both contain 45.6 mg per 12-oz can. The average can of caffeinated soda has about half the caffeine of a cup of coffee. Soft drinks not containing cola, such as 7-Up, ginger ale, and root beer, are all caffeine-free (data from the National Soft Drink Asssociation, Institute of Food Technologists, Washington, DC, 1983).

TABLE 3.—*Coffeine Content of Soda Beveroges**

Beverage	*Caffeine, mg*
Jolt	100.0
Sugar-Free Mr. Pibb	58.8
Mountain Dew	54.0
Mello Yello	52.8
Tab	46.8
Coca-Cola	45.6
Diet Coke	45.6
Shasta Cola	44.4
Shasta Cherry Cola	44.4
Shasta Diet Cola	44.4
Mr. Pibb	40.8
Dr Pepper	39.6
Pepsi Cola	38.4
Aspen	36.0
Diet Pepsi	36.0
Pepsi Light	36.0
RC Cola	36.0
Diet RC	36.0
Diet Rite	36.0
Canada Dry Cola	30.0
Canada Dry Diet Cola	1.2
7 Up, ginger ale, root beer, tonic water, seltzer	0

*Data from the National Soft Drink Association, Institute of Food Technologists, Washington, DC, 1983.

Chocolate accounts for only a fraction of the total caffeine intake. A bar of chocolate ranges from 6 to 26 mg of caffeine per oz, and chocolate milk and cocoa have only small amounts of caffeine.

Many prescription and over-the-counter drugs contain caffeine (Table 4).[6] The analgesic effect of many compounds has been reported to be improved with the addition of caffeine. Caffeine-containing prescription drugs of note include Cafergot (ergotamine tartrate and caffeine), Darvon Compound-65 (propoxyphene hydrochloride, aspirin, and caffeine), and Fiorinal (butalbital, aspirin, and caffeine). Over-the-counter stimulants include the college student staples of No Doz and Vivarin. The danger in these is not the caffeine content but the possibility of drug interactions with other ingredients in over-the-counter drugs. One of the more well-known examples is the synergistic combination of caffeine and phenylpropanolamine (ephedrine), which has been associated with severe hypertension, stroke, and myocardial infarction.

Physiologic Effects of Caffeine

The caffeine molecule, 1,3,7-trimethylxanthine, chemically closely resembles other metabolically important compounds such as the purines (adenine, guanine), adenosine, xanthine, and uric acid. Caffeine is 99% absorbed from beverages and reaches peak concentrations in the serum in 30 to 60 minutes.[2] It is lipophilic, penetrates all biologic membranes, and distributes to all body tissues.[2] It does not accumulate in any organs or tissues. Caffeine readily crosses the blood-brain barrier and the placenta. It is also present in breast milk.

Caffeine is extensively metabolized in the liver through a complex process mediated primarily by the microsomal cytochrome P-450 reductase system. From 2% to 3% is excreted unchanged in the urine. The rate of caffeine metabolism varies, with half-lives ranging from 2 to 12 hours and an average half-life of 4 to 6 hours (about 15% metabolized per

TABLE 4.—*Coffeine Content of Common Drugs**

Drug (Manufacturer)	*Generic*	*Caffeine, mg*
Prescription		
Cafergot (Sandoz Pharmaceuticals)	Ergotamine tartrate, caffeine	100.0
Darvon Compound-65 (Eli Lilly and Co)	Propoxyphene HCl, aspirin, caffeine	32.4
Fiorinal (Sandoz Pharmaceuticals)	Butalbital, aspirin, caffeine	40.0
Over the Counter		
Stimulants		
Caffedrine	Caffeine	200.0
No Doz (Bristol-Myers Products)	Caffeine	100.0 and 200.0
Vivarin (SmithKline Beecham)	Caffeine colloid	200.0
Menstrual		
Midol (Glenbrook)	Acetaminophen, caffeine, pyrilamine maleate	32.0
Analgesics		
Excedrin Extra Strength (Bristol-Myers Products), 2 capsules	Acetaminophen, aspirin, caffeine	130.0
Anacin, Maximum Strength (Whitehall), 2 tablets	Aspirin, caffeine	64.0
Cold Preparations		
Vanquish (Glenbrook)	Aspirin, acetaminophen, caffeine, magnesium hydroxide	33.0
Cope (Glenbrook)	Aspirin, caffeine	32.0
Triaminicin (Sandoz Pharmaceuticals)	Phenylpropanolanine HCl, chlorpheniramine maleate, acetaminophen	30.0

HCl = hydrochloride

*From Bunker and McWilliams.[6]

hour). Longer half-lives are seen in patients with chronic liver disease and in pregnancy.[2] Shorter half-lives are seen in smokers.[2] Smoking accelerates caffeine metabolism, and patients who stop smoking can have doubling of caffeine concentrations in the blood, which may contribute to smoking withdrawal symptoms.

It was initially thought that caffeine and other methylxanthines acted primarily as phosphodiesterase inhibitors. Although they do have this action, it is clearly not their primary effect, and the phosphodiesterase inhibition is minimal at typical serum levels. At present it appears that the most important mechanism of action of caffeine is the antagonism of adenosine receptors.

Adenosine is a locally released purine hormone that acts on two different receptors, A1 and A2. Receptors mediate either an increase or a decrease in cellular concentrations of cyclic adenosine monophosphate. High-affinity (A1) receptors inhibit adenylate cyclase; low-affinity (A2) receptors stimulate adenylate cyclase. The interplay between the two receptors is the subject of much current research. Adenosine receptors are found throughout the body, including the brain, the heart and blood vessels, the respiratory tract, kidneys, adipose tissue, and the gastrointestinal tract.

Adenosine acts locally as a vasodilator. It also reduces platelet aggregation in vitro, inhibits catecholamine and renin release, and inhibits lipolysis. Caffeine nonselectively blocks both adenosine receptors and competitively inhibits the action of adenosine.

When caffeine is consumed at regular intervals, tolerance develops within hours to days.[7] In animals, tolerance is associated with increased adenosine receptor activity and a shift of A1 receptors to the high-affinity state (an increased functional sensitivity to adenosine) and a decrease of β-adrenergic receptor activity.[8] These actions provide a mechanism for the caffeine withdrawal syndrome. Because tolerance occurs rapidly, the effect of caffeine on a person depends on how much caffeine is usually consumed. Recent data have shown that despite the tolerance that develops, the regular consumption of 6 to 11 cups of coffee per day may produce persistent small elevations in norepinephrine levels and free fatty acid release after caffeine metabolism is saturated.[9]

Caffeine and Coffee Caveats

Problems in Research

The literature on caffeine is voluminous, and recurrent flaws are evident in the research. For example, many studies in animals use doses that are hundreds to thousands of times those achieved by normal human consumption. Extrapolating the results of this work to human consumption is obviously problematic. Also, whereas most humans are caffeine tolerant, most animals are not conditioned when studied.

In humans, studies with coffee and caffeine are complicated by many extraneous factors. Coffee consumption seems to correlate with many variables: social class, race, religion, psychological state, and coronary artery disease risk factors.[1] All of these factors confuse the question of whether caffeine or coffee is the cause within an association when one is found. For example, many studies have verified that coffee consumption increases with education and income. White persons drink about 3½ times more coffee than African Americans.[10] Coffee consumption is highly correlated with membership in the Catholic Church.[11] Mormons and Seventh-Day Adventists, in keeping with church doctrine, consume much less coffee than do others in similar geographic areas.[12] In Mormons and Seventh-Day Adventists, a reduced risk of malignancy has been well documented. This is confounded, however, by the reduced smoking and alcohol intake practiced by these groups. Coffee intake is positively correlated with a diagnosis of depression and with various measures of stress and anxiety.[13]

Another general problem with caffeine and coffee research is the interchange of the two substances. Data from studies of animals and human physiologic data gathered using pure caffeine are often extrapolated and used in research questions that involve coffee, without considering the other compounds that are part of the coffee brew.

Physiologic Effects of Caffeine

Central Nervous System Effects

Caffeine acts principally as a stimulant. A dose of two cups of coffee increases vigilance and arousal. For example, generalized motor activity in young boys increases after two cups of coffee. Caffeine also reduces fatigue. Complex motor tasks, however, are disrupted. Of interest, the slowed reaction time induced by alcohol consumption is potentiated by caffeine ingestion, so coffee is not an "antidote" for intoxication.[2,14]

Caffeine also has substantial effects on sleep. Ingesting caffeine 30 to 60 minutes before sleep will increase sleep latency, decrease total sleep time, and substantially worsen subjective estimations of sleep quality. There are large variations in sensitivity to sleep disturbance, with the effects being greater in persons who do not drink caffeinated beverages regularly.[15]

Caffeine also leads to a reduction in cerebral blood flow, and several studies have now shown that blood flow is decreased by caffeine-induced cerebrovascular vasoconstriction.[16,17]

A key behavioral effect of caffeine is reinforcement. In healthy subjects, as the caffeine content per cup of coffee decreases, the number of cups consumed increases. Caffeine also may be a determinant of nicotine consumption. It has been reported that compared with regular coffee, drinking decaffeinated coffee leads to an increase in the number of cigarettes smoked by volunteers.[18] This, coupled with nicotine's ability to accelerate caffeine metabolism, leads to a reinforcing cycle between caffeine and smoking.

A caffeine withdrawal syndrome is well described. Withdrawal symptoms include headache and fatigue most prominently; anxiety, impaired psychomotor performance, nausea and vomiting, or an intense desire for coffee occur less commonly.[19] Headache is usually preceded by a feeling of fullness in the head that occurs about 18 hours after the last caffeine intake. This is followed by a diffuse, throbbing headache that worsens with exercise.

Cardiovascular Effects

There are many contradictions in the literature regarding the effect of caffeine on heart rate, blood pressure, and plasma catecholamine levels.[7,20-25] Recent data have clearly shown that the systolic blood pressure increases abruptly about 10 mm of mercury with caffeine. The heart rate slows for about an hour, then increases for two to three hours thereafter. Tolerance to caffeine develops quickly, however. Long-

term ingestion has little or no effect on the blood pressure, heart rate, or catecholamine levels.[24]

Respiratory Effects

The primary respiratory effect is an increase in the respiratory rate. Careful studies have shown that the respiratory rate correlates closely with the plasma caffeine level.[24] Caffeine has been used successfully as a stimulant in neonates to prevent recurrent apneic episodes. While the precise mechanism for caffeine's respirogenic effect is unknown, there appears to be an increased sensitivity of the medullary respiratory center to carbon dioxide.[2]

In patients with asthma, caffeine functions as a bronchodilator. Bronchodilation is only about 40% of the potency of theophylline at comparable concentrations.[26] At similar doses, caffeine has more central nervous system toxicity as well.

Endocrine and Metabolic Effects

Caffeine increases circulating catecholamine levels, and, partially through this mechanism, it increases the basal metabolic rate. Lipolysis with the release of free fatty acids occurs, and serum free fatty acid levels rise to 50% to 100% above normal. This is most likely a consequence of systemic catecholamines or may result from a local antagonism of adenosine inhibition of lipolysis.

The effect of caffeine on blood glucose has been the subject of debate. Most studies have shown that caffeine does not appreciably increase blood glucose levels in healthy people.

Debate has raged over the role of coffee and caffeine in cholesterol metabolism. Some, but not all, epidemiologic studies find an association between long-term coffee consumption and increased serum cholesterol levels. Most of the evidence in support of a coffee-cholesterol connection has come from overseas, namely Australia, Israel, Finland, Sweden, and Norway, the home of the Tromsø Heart Study.

In Tromsø more than 14,000 Norwegians were questioned, and a strong dose-response relationship between coffee consumption and serum cholesterol levels was found.[27,28] These data showed a linear relationship for both women and men, with serum cholesterol levels increasing about 30 mg per dl as coffee intake increased from zero to more than nine cups per day (Figure 1). Soon after the Tromsø reports, large epidemiologic studies from Evans County, Georgia, and Framingham, Massachusetts, failed to show this correlation in the United States.[29] Other studies that did show a correlation failed to show a dose-response relationship.

An interesting study from Stanford (California) Medical School in 1985 reported that consuming two to three cups per day of coffee seemed to correlate with higher levels of apolipoprotein B, leading some to speculate that this might be the mechanism of cholesterol elevation.[30]

Serutiny of the coffee-cholesterol relationship by several researchers revealed that the method of brewing appeared to have a considerable effect on the cholesterol-raising ability of coffee.[27,31,32] The predominant method of brewing coffee in Norway is by boiling, in contrast to the percolated or instant methods in the United States. In several studies that have compared boiled and filtered coffee, boiled coffee had a stronger effect on cholesterol levels in almost all cases.[32] A surfactant coffee factor has been identified that is precipitated by hard water and removed by filtration, and there has been speculation that this surfactant might be responsible for the changes observed in the Tromsø study.[33] Others have proposed that the temperature difference of boiled coffee, which is kept at higher temperatures for longer periods of time, frees some "agent" that raises cholesterol levels.[33] Most recent epidemiologic data have shown no difference in total cholesterol or low-density lipoprotein levels between persons who drink boiled coffee and those who consume filtered coffee.[33]

It must be kept in mind that coffee, rather than caffeine, has been the target of many of the epidemiologic studies. In

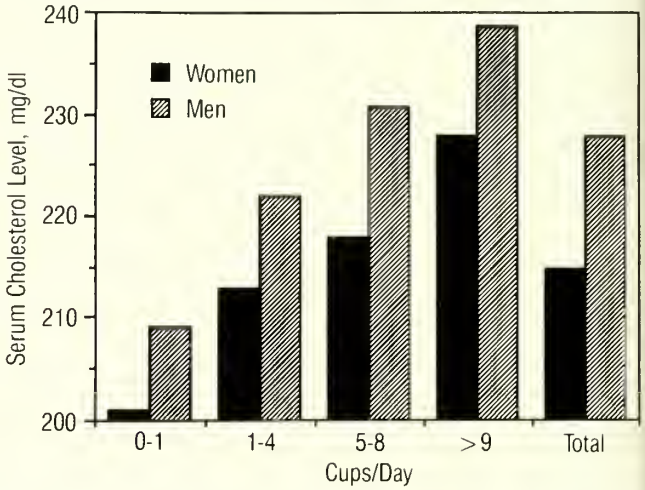

Figure 1.—Serum cholesterol levels were measured versus cups of coffee consumed per day as determined by a survey of more than 14,000 Norwegians demonstrating a strong dose-response relationship (adapted from Thelle et al[27]).

fact, in several studies showing a coffee-cholesterol connection, the caffeine-equivalent dose of tea did not have the same effect. In addition, the same effects on cholesterol and low-density lipoprotein levels have been reported with decaffeinated coffee.

At present, the role of caffeine in causing an increase in cholesterol levels is tenuous. It is more likely that a relationship exists between a non-caffeine component of coffee and serum cholesterol and low-density lipoprotein levels. There are also confounding factors such as the brewing method and associated risks found in coffee drinkers, such as saturated fat intake, that still need to be evaluated.

Gastrointestinal Effects

In the gastrointestinal tract, caffeine stimulates the small intestine to secrete water and sodium. Of interest, coffee does not have this effect, suggesting that there is some interfering substance present. In the distal colon, coffee stimulates motility and promotes defecation. As the same effect is seen with decaffeinated coffee, it is unlikely to be mediated by caffeine.

Since the 1940s, it has been known that coffee stimulates the secretion of gastric acid and pepsin. Caffeine has a direct effect on gastric acid secretion. In a now-famous study, Cohen and Booth at the University of Pennsylvania examined the dose-response relationships between caffeine, regular and decaffeinated coffee, and gastric acid secretion and lower esophageal sphincter pressure in normal subjects.[34] Eight subjects were administered caffeinated coffee, decaffeinated coffee, pure caffeine, or distilled water by nasogastric tube after an eight-hour fast. The response in peak acid

output was higher with both regular and decaffeinated coffee than with pure caffeine (Figure 2). The difference at the higher doses between either the regular or decaffeinated coffee and caffeine was statistically significant. A similar difference was found on manometric measurement of the lower esophageal sphincter tone. In order of potency, regular coffee, then decaffeinated coffee, and then pure caffeine decreased the tone. To date, the ingredient in coffee responsible for these effects on gastric acid secretion and lower esophageal sphincter tone has not been identified. Based on these findings, decaffeinated coffee is not an alternative for patients with peptic ulcer disease or gastroesophageal reflux.

Caffeine and Coffee Consumption in Human Disease

Many diseases have been associated with caffeine and coffee consumption. Caffeine and coffee intake have often been associated with hypertension. Blood pressure, as discussed earlier, changes initially but shows little abnormality in the long term.

The use of caffeine in pregnancy has long been debated. Studies of animals have shown that caffeine can retard fetal growth and cause skeletal abnormalities at doses equivalent to 12 to 24 cups of coffee per day.[35] In humans, retrospective epidemiologic studies in the 1970s found an increased incidence of birth defects and low birth weights with coffee consumption and led the Food and Drug Administration to remove caffeine from the "Generally Regarded as Safe" list of substances in 1980.[36] Large epidemiologic studies since then have not supported this concern. Despite this, most obstetricians at present recommend that caffeine intake be limited to less than 400 mg per day during pregnancy.[36]

A dose-response relationship between coffee intake and premenstrual syndrome has been reported.[37] This has led

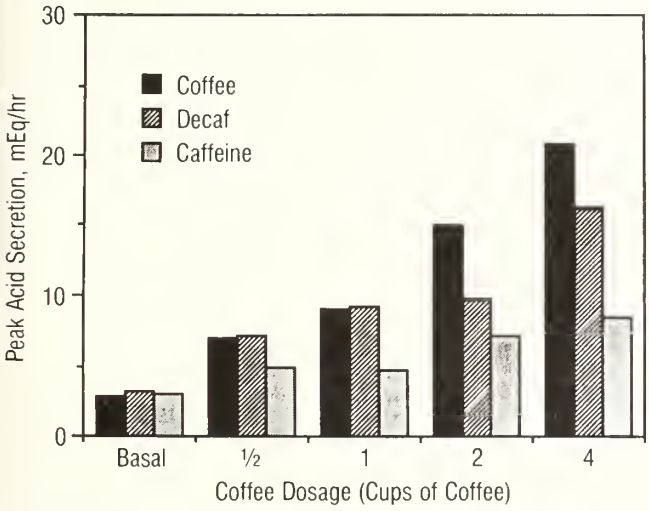

Figure 2.—The graph shows peak gastric acid response to regular coffee, decaffeinated coffee (Decaf), and equivalent doses of caffeine (adapted from Cohen and Booth[34]).

many to recommend that those who suffer from premenstrual symptoms abstain from caffeine.

As mentioned earlier, coffee decreases the lower esophageal sphincter tone and hence promotes gastroesophageal reflux. It is interesting to note that coffee also seems to have a direct irritant effect when infused into the esophagus. Peptic ulcer disease and caffeine intake were first linked in the 1950s. In 1974 in a large study of 11,000 male college students, a positive correlation was reported between coffee consumption and peptic ulcer disease later in life.[38] Other studies have failed to show a correlation. Nevertheless, it is common practice to recommend that patients who have peptic ulcer disease avoid drinking either regular or decaffeinated coffee.

Caffeine is well known to cause nervousness, restlessness, anxiety, and insomnia. It has also been reported to aggravate psychiatric disease. A disorder known as "caffeinism" was first described in 1974 and is currently listed in the *Diagnostic and Statistical Manual of Mental Disorders.*[39,40] It is defined as a state in which high doses of caffeine acutely manifest as frequent urination, jitteriness, lightheadedness, irregular heartbeat and breathing, upset stomach, diarrhea, and heartburn.

An interesting and fortunately rare occurrence is caffeine overdose. In high doses, caffeine causes hypotension from vasodilation (β-adrenergic mediated) and pronounced tachycardia with massive systemic catecholamine release. Deaths have been reported after the intravenous, oral, and rectal administration of caffeine or coffee,[2] the lethal dose being about 10 grams or 170 mg per kg, which is equivalent to 75 cups of coffee, 125 cups of tea, or 200 cans of cola.

The three principal medical diseases that have received the most notoriety are coronary heart disease, arrhythmia, and pancreatic cancer.

Coronary Heart Disease

Epidemiologic studies have associated coffee consumption with many of the accepted coronary risk factors. In general, the risk factors of greatest concern are cigarette smoking, diabetes mellitus, alcohol abuse, socioeconomic status, and oral contraceptive use.

One of the best-established correlations is between smoking and coffee consumption.[1,41,42] At age 50, only 20% of those who did not drink coffee were smokers. Of those who drank more than ten cups of coffee per day, 71% were smokers. Smoking is particularly associated with coffee intake in young and middle-aged adults. Smoking should be and usually is accounted for in most studies. On the other hand, elevated cholesterol levels and hypertension have had inconsistent associations with caffeine or coffee intake, and there is little evidence to support controlling for these in large clinical studies.

Other known risk factors probably have less of an effect. There is little evidence supporting an association between coffee and diabetes mellitus.[2,43] In many studies, alcohol use in moderation has been found to be negatively associated with the risk of coronary artery disease. Alcohol use is most often positively correlated with coffee consumption.[41] Therefore, some authors suggest that it should be controlled for in coffee-coronary heart disease studies.[1] Oral contraceptive use clearly increases the risk of coronary disease in women of reproductive age. Oral contraceptive use has been related to cigarette smoking, but its relation to coffee use is unknown. But because coffee drinking and cigarette smoking are so closely linked, many authors think that oral contraceptive use and coffee consumption are associated and should be controlled for.[1] Clearly the role of oral contraceptives in the larger picture of coronary heart disease is small in comparison to smoking and other risk factors.

Bearing the confounding associations among known risk factors in mind, the data from the studies that have reported an association between coffee consumption and coronary

heart disease can be critically examined. The first report of an association between coffee consumption and ischemic heart disease was published in 1963.[44] It was based on data from an eight-year prospective study of 2,000 male employees of the Western Electric Company in Chicago, Illinois. Those who consumed five cups or more of coffee per day were reported to have higher rates of angina and myocardial infarction than men consuming less. Initially it was suggested that the sugar in coffee was to blame. Later it was shown that the association between coffee consumption and ischemic heart disease could be accounted for by cigarette smoking alone. Nevertheless, this study sparked a controversy that has persisted.

In 1972 the Boston Collaborative Drug Surveillance Program published its results based on 276 patients with 1,104 matched controls drawn from hospitals around the world.[45] It found that drinking more than six cups of coffee a day was associated with a more than twofold increased risk of myocardial infarction that could not be accounted for by smoking. The increased risk held up when data were analyzed separately for smoking, sex, and age. No association with tea drinking was found, implying that a component of coffee other than caffeine was responsible.

A second more comprehensive study by the Boston Program, involving about 13,000 hospital inpatients, including 440 with the diagnosis of myocardial infarction, confirmed a greater than twofold increased risk among patients who consumed more than six cups of coffee a day.[46,47] Relative risks were 1.6 for those drinking one to five cups per day and 1.9 for those drinking six cups or more. Again, no association with tea was found, exonerating caffeine as the factor.

These reports from Boston were immediately followed by studies from Britain that supported the coffee-coronary disease connection.[48] In the wake of these studies, which generated considerable interest, more than a dozen studies, both retrospective and prospective, have since failed to show an association between coffee consumption and coronary heart disease (Table 5).[29,31,43,49-55]

By 1983 the preponderance of negative studies was overwhelming. Strong arguments were made by Klatsky and the group at the Oakland (California) Kaiser Foundation Medical Center, reporting on patients with myocardial infarction, who showed no difference in coffee consumption compared with matched controls in interview studies.[49] In addition, the Framingham study included more than 4,000 patients and found no evidence for an association.[29,57]

Then in 1986 LaCroix and co-workers reported the results of a 25-year study of 1,130 male Johns Hopkins University (Baltimore, Maryland) medical students with multiple, repeated measures of caffeine intake over the years.[55] They showed a strong dose-response relationship between coffee consumption and the risk of coronary heart disease. Relative risks ranged from 1.3 for one or two cups to 2.5 for more than five cups of coffee per day compared with drinking no coffee at all. The study controlled for smoking but not for other life-style factors that may be associated with coronary disease, such as diet high in total and saturated fats, high serum cholesterol levels, a sedentary life-style, and high levels of occupational stress. These data once again brought into question the long-term effects of coffee drinking.

Recently Klatsky and associates reported a vast cohort study of Kaiser Foundation patients and concluded that heavy coffee intake may increase the risk of coronary artery disease, reversing their earlier conclusions reported in the 1970s.[58] More than 100,000 patients, including 1,914 patients with coronary disease, admitted between 1978 and 1985 were examined. Patients completed questionnaires about sociodemographic traits, habits, and health as well as health measurements and laboratory test results. The median follow-up was five years. Compared with noncoffee drinkers, the following relative risks were found: 1.1 for one to three cups, 1.4 for four to six cups and 1.4 for more than six cups per day. There was no clear dose-response relationship, however, and, again, tea consumption was not related to myocardial infarction or other coronary events. The authors concluded that a weak, independent correlation of coffee use to acute myocardial infarction existed, not mediated by an effect on blood cholesterol levels.[58] They recommended that persons at risk for myocardial infarction should consider limiting their coffee intake to less than four cups per day.

Another recent large prospective study was reported by Grobbee and colleagues (The Health Professionals Follow-up Study).[31] They examined the risk of myocardial infarction, the need for bypass grafting or percutaneous angioplasty, and the risk of stroke in more than 45,589 men. None of those studied had a history of heart disease. Participants were mailed questionnaires in 1986, and 33% of the eligible group responded. No correlation was found between coronary disease and coffee or caffeine consumption, with an age-adjusted relative risk for more than four cups per day of 1.04.

This study has received many criticisms, some criticizing

TABLE 5.—*Studies Failing to Find an Effect of Coffee or Caffeine Consumption on Coronary Artery Disease Following the Boston Collaborative Drug Surveillance Program*

Reference	*Patients, No.*	*Description*
Klatsky et al, 1973[49]	464	Matched case-control study of patients with MI
Dawber et al, 1974[29]	1,992 men 2,500 women	12 years' follow-up of men and women from Framingham, Mass, data base
Hennekens et al, 1976[43]	649	Interviewed wives of patients with sudden death
Yano et al, 1977[50]	7,705	Cohort study of Japanese-Hawaiian men observed for 6 years
Heyden et al, 1978[51]	2,530	Cohort was observed for 4.5 years in Evans County, Georgia
Rosenberg et al, 1980[52]	487	Case-control study of women after an MI
Murray et al, 1981[53]	17,000	Observed Lutheran Brotherhood for 11.5 years
Welin et al, 1984[54]	834	Prospective study of 50-year-old Swedish men
LaCroix et al, 1986[55]	1,130	Prospective study examining male medical students over 25 years
Yano et al, 1987[56]	7,705	Reexamined Japanese-Hawaiian cohort and again found no association
Grobbee et al, 1990[31]	45,589	Prospectively studied risk of MI or revascularization in men

MI = myocardial infarction

TABLE 6.—*Studies That Fail to Correlate Coffee Intake and Arrhythmia*

Reference	*Description of Study*
Newcombe et al, 1988[63]	Caffeine (500 mg) given to 34 normal persons; no increase in ventricular arrhythmias on a 24-hour Holter recording
Myers et al, 1988[64]	A randomized, placebo-controlled, within-patient, crossover study design of postinfarction patients given 300 mg of caffeine
Myers et al, 1990[65]	35 patients after infarction received 300 mg of caffeine followed by a second 150-mg bolus after 4 hours
Graboys et al, 1989[66]	Single-blind, crossover study of patients with history of malignant ventricular arrhythmias given 200 mg of caffeine
Chelsky et al, 1990[67]	Electrophysiologic study of 22 patients with a history of symptomatic nonsustained or sustained ventricular tachycardia or ventricular fibrillation; patients were studied before and 1 hour after coffee ingestion with 275 mg of caffeine

the 33% response rate to the initial questionnaire. Also, the authors did not fully explore the more-than-five-cup threshold that was found by LaCroix and others to be associated with coronary disease.[55,59] The study was also criticized for excluding patients who had coronary disease at the initial questioning. It may well be that the excluded cohort represented those who had already suffered from and were sensitive to the effects of coffee or caffeine, as the age of the cohort started at 40 and ended at 75. Also, there was no review of past habits of coffee consumption. LaCroix's medical student study[55] suggested a long-term effect (25 years) that Grobbee and co-workers did not address.

In summary, the evidence to date that coffee or caffeine intake at normal levels is correlated with coronary heart disease is inconsistent. The long-term effects of coffee use are still not clear. The recent work of LaCroix and colleagues does raise the question of whether coffee drinking produces effects that may manifest only after several decades. Heavy caffeine use (>4 cups per day of coffee) may be associated with coronary artery disease and needs further investigation.

Arrhythmia

Although there is much anecdotal acceptance that there is an association between caffeine intake and arrhythmia, the literature contains little evidence to support this. Studies using animals have shown that caffeine in massive doses can reduce the ventricular fibrillation threshold and alter electrical excitation in cultured cardiac cells.[60] There have also been many studies in the literature that examine this question in humans.

Prineas and colleagues measured ventricular extrasystoles in 7,311 subjects who had a two-minute single-lead electrocardiogram done as part of a coronary risk factor screening program.[61] They found that persons who drank nine or more cups of coffee or the equivalent amount of tea a day were more likely to have at least one premature ventricular beat. Their data showed a poor dose-response relationship, however.

Dobmeyer and associates performed electrophysiologic studies in 7 healthy volunteers and 12 patients with heart disease.[62] Caffeine use did not affect cardiac conduction but did alter some of the electrophysiologic measurements. The authors concluded that caffeine exerted little or no effect on cardiac conduction but might aggravate an existing predilection to arrhythmia.

Many subsequent negative studies confirmed these conclusions (Table 6).[63-67] They include careful dose-response studies in patients with malignant arrhythmias and in those who had had myocardial infarction,[63,64] as well as an electrophysiologic analysis in which low doses of caffeine were given to patients with known arrhythmia.[67]

The evidence is thus mounting that the common recommendation to avoid caffeine use when patients have "arrhythmias" is not warranted. Myers in a recent review article summarizes this opinion:

> [M]oderate ingestion of caffeine does not increase the frequency or severity of ventricular arrhythmias in normal persons, patients with ischemic heart disease, or those with pre-existing serious ventricular ectopy.[68(p149)]

Pancreatic Cancer

Caffeine or coffee intake have been implicated in many solid tumors such as pancreatic cancer, urinary tract cancer (most notably bladder cancer), renal cell carcinoma, ovarian cancers, and breast cancer. Confounding risk factors, recall bias, and small numbers have usually precluded making definitive statements on these tumors.

The suggestion that pancreatic cancer may be associated with coffee consumption emerged from several "ecologic" studies (Table 7).[69-74] These typically searched for positive correlations between coffee consumption or coffee importation and national pancreatic cancer mortality rates. Remarkably, mortality rates from pancreatic cancer tracked coffee use trends consistently, with a ten-year lag in most studies (Table 7). Several of these studies showed a clear correlation, but these could only be considered at best a suggestion of a direct link.

Then in 1981 MacMahon and colleagues published a case-controlled interview study of 369 patients with pancreatic cancer, investigating how much coffee or tea they consumed before diagnosis.[75] Their answers were compared with those of a control group of 644 hospital inpatients without pancreatic cancer. A significant increase in cancer prevalence among coffee drinkers, but not among tea drinkers, was found. The overall risk ratio was 1.8 (95% confidence limits, 1.0 to 3.0). The dose-response relationship was statistically significant only in women.

The selection of controls in this study has been criticized because 40% had chronic gastrointestinal disease, which may have led to lower caffeine intake. Also, the control group was skewed by the exclusion of smoking and alcoholic patients, which may have eliminated heavy coffee drinkers as well.[2] Others emphasized that the duration of coffee consumption needs to be considered, as do other variables such as coffee additives. Also puzzling was the fact that the dose-response relationship was only present for women.

A plethora of studies have since examined the question of a link between coffee drinking and pancreatic cancer. A total of 18 case-control studies carried out between 1981 and 1990 have yielded both affirming and negating results (Table 8).[76-83] Although the case-control studies have not been conclusive, existing prospective studies have been consistent in their findings: none of the six prospective investigations performed between 1983 and 1990 that examined coffee intake and risk of pancreatic cancer (Table 9)[84-89] have shown an association.

In summary, many of the studies that have found a corre-

TABLE 7.—*Ecologic Studies Correloting Poncreotic Cancer and Coffee Intoke*

Reference	*Description of Study*
Stocks, 1970[69]	Correlated death rates from cancers with several variables including coffee in 20 countries; positive correlation between pancreatic cancer and coffee drinking in men
Cuckle and Kinlen, 1981[70]	Found significant correlations between coffee consumption patterns for 16 countries and pancreatic cancer mortality rates
Spector, 1981[71]	Found trend in coffee imports tracked with pancreatic cancer death rates between 1948 and 1978 in the United Kingdom
Benarde and Weiss, 1982[72]	Found per capita coffee consumption patterns for the United States from 1950 to 1980 were tracked by pancreatic cancer incidence rates offset by 10 years
Binstock et al, 1983[73]	Found per capita coffee imports from 1957 to 1965 in 22 countries correlated with pancreatic cancer death rates in 1971 to 1974
La et al, 1987[74]	Found moderate correlation between coffee consumption and pancreatic cancer mortality in 20 Italian regions

TABLE 8.—*Cose-Control Studies Examining Pancreatic Cancer and Coffee Intoke*

Reference	*Patients, No.*	*Description of Study*
Jick and Dinan, 1981[76]	78	Pancreatic cancer patients, with hospital inpatients as controls, were interviewed; no association was found
Lin and Kessler, 1981[77]	109	Found that patients with pancreatic cancer drank more decaffeinated coffee than did controls
Goldstein, 1982[78]	45	Reviewed coffee history in the charts of pancreatic cancer patients and found no correlations when compared with prostate and breast cancers
Severson et al, 1982[79]	22	Case-control study addressing asbestos in drinking water found no correlation
Wynder et al, 1983[80]	275	No correlation found
Kinlen and McPherson, 1984[81]	216	Pancreatic cancer patients compared with other cancer patients; no correlation found
Gold et al, 1985[82]	274	Patients interviewed and matched to controls; no association found
Hsieh et al, 1986[83]	176	Patients compared with hospital controls; slight increase for heaviest consumption found, but no dose response

MI = myocardial infarction

lation between coffee drinking and pancreatic cancer have been limited. All are retrospective case-control studies. Although there is a correlation at a national level between coffee consumption and pancreatic cancer mortality rates, there is little evidence at this time that coffee directly contributes to pancreatic cancer.

Summary

Caffeine is a methylxanthine whose primary biologic effect is antagonism of the adenosine receptor. Its presence in coffee, tea, soda beverages, chocolate, and many prescription and over-the-counter drugs makes it the most commonly consumed stimulant drug. Initially caffeine increases blood pressure, plasma catecholamine levels, plasma renin activity, serum free fatty acid levels, urine production, and gastric acid secretion. Its long-term effects have been more difficult to substantiate.

Most of the caffeine consumed in the United States is in coffee, which contains many other chemicals that may have other biologic actions. The consumption of coffee is a self-reinforcing behavior, and caffeine dependence and addiction are common.

Coffee and caffeine intake have been linked to many illnesses, but definitive correlations have been difficult to substantiate. Initial trials showing coffee's association with coronary disease and myocardial infarction have been difficult to reproduce and have many confounding variables. Recent studies showing a larger effect over long follow-up periods and with heavy coffee consumption have again brought the question of the role of coffee in disease states to the fore. Caffeine in average dosages does not seem to increase the risk of arrhythmia. At present there is no convincing evidence that caffeine or coffee consumption increases the risk for any solid tumor.

The intake of coffee and caffeine has clearly been decreasing in this country over the past two decades, largely brought about by the increasing health consciousness of Americans. Although there have been many studies that hint that the fears of increased disease with coffee drinking may be warranted, many questions have yet to be answered about the health effects of coffee and caffeine use.

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TABLE 9.—*Prospective Studies Exomining Poncreatic Cancer ond Coffee Intoke*

Reference	*Potients, No.*	*Description of Study*
Heuch et al, 1983[84]	16,713	Prospective study of Norwegians who received dietary questionnaires in 1967 and were followed up in 1978; relative risks for coffee intake were all <1.0
Snowden and Phillips, 1984[85]	23,912	Observed Seventh-Day Adventists between 1960 and 1980 and found no increase in risk
Whittemore et al, 1985[86]	50,000	Male former students from University of Pennsylvania and Harvard University observed from ages 16 to 50 years; found no association between coffee drinking while in college and later pancreatic cancer
Nomura et al, 1986[87]	7,355	Prospective study of Japanese men on Oahu, Hawaii, who had 24-hour dietary surveys done in 1965 to 1968 and were observed until 1983; coffee intake not found associated with increased risk
Mills et al, 1988[88]	34,000	Observed California Seventh-Day Adventists from 1976 to 1983; no increased risk associated with coffee consumption
Hiatt et al, 1988[89]	122,894	Kaiser group with 6-year follow-up; no increase in risk found associated with coffee

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Urinary Tract Infections in Children
An Update

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Urinary tract infection is a common and frequently recurring condition in children. The susceptibility of the host, the presence of urinary tract abnormalities, and the virulence of the urinary pathogens are of primary importance in the development of the infection. Renal parenchymal scarring, hypertension, and renal insufficiency are well-established complications of the infection in children. To reduce the risk of renal damage, diagnosis and treatment must be prompt. The diagnosis demands radiologic evaluation of the urinary tract in all boys, all children younger than 5 years, all patients with voiding dysfunction, and school-aged girls with recurrent infection to identify those patients with vesicoureteral reflux, obstruction, or other urinary tract abnormalities. Both voiding cystourethrography and renal ultrasonography are the initial examinations to use to determine the next appropriate study. Children with vesicoureteral reflux or with recurrent urinary tract infections should receive prophylactic antibiotic therapy and should be observed closely to prevent renal scarring.

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Urinary tract infection (UTI) occurs in as many as 5% of female and 1% to 2% of male children.[1-3] Although most children respond to therapy without having significant sequelae, severe infection may result in renal scarring, hypertension, or compromised renal function.[2,4] In this review we describe various aspects of this condition in children. Special emphasis is given to current concepts in the pathophysiology of UTI and to the diagnostic evaluation, management, and prognosis of children with UTI or asymptomatic bacteriuria.

Description and Definitions

The diagnosis of asymptomatic (covert) bacteriuria is made when an asymptomatic child has cultures of two properly obtained, clean-voided, midstream urine specimens growing 10^5 colonies or more per milliliter of a single organism, a catheterized specimen growing more than 10^3 colonies per milliliter, or a specimen obtained by suprapubic aspiration growing any number of colonies. Urinary tract infection is diagnosed when a symptomatic child has a culture of one properly obtained, clean-voided, midstream urine specimen growing 10^5 colonies or more per milliliter of a single organism, a catheterized specimen growing more than 10^3 colonies per milliliter, or a specimen obtained by suprapubic tap growing any number of colonies.

Urinary tract infection is generally subdivided into two categories: uncomplicated (lower tract infection or cystitis) and complicated (upper tract infection or pyelonephritis).[5,6] Some conditions associated with complicated UTI in children are vesicoureteral reflux, obstructive uropathy, neurogenic bladder, voiding dysfunction, renal calculi, systemic diseases such as diabetes mellitus, diseases associated with immunologic defects, and the presence of an indwelling catheter or nephrostomy tube.

Etiology

Gram-negative enteric bacteria are the most common organisms causing UTI[5-7]; *Escherichia coli* accounts for 80% of the cases. Other important organisms, especially in neonates and in complicated cases, are *Proteus mirabilis* (common in boys), *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter* species, *Staphylococcus aureus* (especially in older children), *Streptococcus viridans*, enterococci, and *Candida albicans*.[5-7] Uncomplicated UTI is usually caused by a single organism, whereas in patients with complicated UTI, many organisms may be present. Urinary tract infections by urease-producing organisms such as *P mirabilis, K pneumoniae*, and *P aeruginosa*, which alkalinize the urine, predispose to calculous (struvite) formation.[8] Acute hemorrhagic cystitis may be caused by bacteria or an adenovirus. Urethritis (reviewed in detail by Parrott[9]) is diagnosed by the presence of urethral symptoms and low colony counts of less than 10^4 per ml. Gonococci, chlamydia, and *Ureaplasma urealyticum* are common etiologic agents.

Pathophysiology

The susceptibility of the host and the virulence of the invading bacteria are of primary importance in the development of UTI.[1,10,11] Young age, female sex, abnormal defense mechanisms, the presence of urinary tract abnormalities, sexual activity, and instrumentation are the main host-related factors that contribute to the development of UTI.[1,10,11]

In most cases bacteria ascend the urinary tract following perineal colonization. In neonates UTI is often presumed to be hematogenous,[6] although a bacteremia due to upper tract infection often cannot be excluded. The short female urethra and its proximity to fecal flora may, in part, explain the predominance of UTI in girls after the neonatal period. Uncircumcised male infants have an increased incidence of UTI

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ABBREVIATIONS USED IN TEXT

UTI = urinary tract infection
VCUG = voiding cystourethrogra[phy/m]

when compared with circumcised infants.[12,13] An increased periurethral carriage of uropathic organisms such as *E coli* and *P mirabilis* in association with higher bacterial colony counts has been noted in uncircumcised boys.[14,15] It has been hypothesized that circumcision reduces meatal contamination, thereby decreasing bacterial ascent into the bladder. The benefits of neonatal circumcision, however, are the subject of much debate,[16,17] and further prospective studies are needed both to confirm these observations and to assist in recommendations regarding circumcision. Sexual intercourse increases the risk of UTI in adolescent girls.[6,9]

Defense mechanisms protecting against bacterial growth in the urinary tract include complete bladder emptying, phagocytosis, secretory immunoglobulin IgA secretion by the bladder mucosa, and serum antibody production (which may reduce the severity of upper tract infection).[6,11]

Obstruction and urinary stasis, whether anatomic or functional, predispose to infection.[2,10] Posterior urethral valves, obstruction at the ureteropelvic junction or ureterovesical junction, and ectopic ureterocele are the main causes of anatomic obstruction in children.[2,10] Neurogenic bladder is an important cause of recurrent UTI. Incomplete bladder emptying plays a role in the pathogenesis of UTI in patients with neurogenic bladder, voiding dysfunction in those who are otherwise neurologically normal (bladder-sphincter dyssynergia), and in patients with vesicoureteral reflux or large bladder diverticula (aberrant micturition).[10,18,19] An association of constipation with uninhibited bladder contractions and UTI has also been described in children.[20]

Vesicoureteral reflux is found in 30% to 50% of children with UTI[2,21,22] but is rare in normal children.[23] Intrarenal reflux may be the mechanism by which bacteria enter the renal cortex and cause parenchymal infection and scarring. Intrarenal reflux is more common in compound calyces where a concave central portion of the papilla eliminates the obliquity of papillary duct entry.[22,24] Autopsy studies have shown an increased frequency of compound calyces in the upper and lower poles of the kidney. This distribution, in conjunction with the increased likelihood of intrarenal reflux in papillae serving these compound calyces, is thought to explain the bipolar distribution of reflux nephropathy. The likelihood of parenchymal scarring is related to the severity of vesicoureteral reflux.[23,24] The reflux of sterile urine may inhibit renal growth, but it is unlikely to cause parenchymal scarring in the absence of obstruction or dyssynergia.[25,26]

Instrumentation of the urinary tract, prolonged catheter drainage, and indwelling nephrostomy tubes bypass a person's natural defense mechanisms and predispose to asymptomatic bacteriuria or UTI.

The virulence characteristics of the bacteria causing UTI play a major role in the pathogenesis of the infection. Several excellent reviews of this subject have been published.[27-31] A correlation between elevated antibody titer to capsular O and K antigens of *E coli* and renal involvement has been demonstrated.[2] Bacterial adherence is of great importance in the genesis and severity of UTI[11,32] and has been extensively investigated.[28-31,33] Bacteria bind to uroepithelial mucosa by a process called attachment, the result of an interaction between bacterial surface ligands called adhesins and epithelial cell receptors. Adhesins are frequently associated with pili or fimbriae located on the bacterial surface.[28] Most attaching uropathogenic bacteria recognize the globoseries of glycolipid epithelial cell receptors with the common disaccharide galactose α-1-4 galactose-β (Gal-Gal). The pretreatment of bacteria with receptor analogues such as globotetraosylceramide inhibits attachment and aborts the inflammatory response.[33]

There is, furthermore, a relationship between the intensity of inflammatory response to a uropathogenic organism, as measured by temperature, the extent of pyuria, the concentrating ability and elevation of circulating acute-phase reactants, and attachment to Gal-Gal receptors.[29] This may relate to enhancement by attachment of the action of lipid A, the moiety of endotoxin that triggers inflammation. Fimbriated strains of *E coli* are present in 94% of children with pyelonephritis versus 14% to 19% of children with lower UTI.[32] Of interest, in patients with vesicoureteral reflux, pyelonephritic scars have been reported to be more often associated with nonattaching bacteria, suggesting reduced host resistance due to reflux as a contributing factor.[34] Human milk may have a preventive effect on UTI in infants as evidenced by increased concentrations of secretory IgA[35] and neutral oligosaccharides that inhibit bacterial adhesion[36] in the urine of breast-fed infants. Recently immunization with Gal-Gal pili vaccine has been shown to protect against pyelonephritis induced by fimbriated *E coli* in mice.[37]

Epidemiology

The occurrence of UTI varies with age and sex. The prevalence of asymptomatic bacteriuria in neonates ranges from 1% in full-term infants to 3% in premature infants.[1] Symptomatic UTI in the neonatal period has a prevalence of 0.14%. In the neonatal age group there is a male predominance whereas female predominance occurs afterwards.[38] The prevalence of asymptomatic bacteriuria is 1% of preschool children, 1.2% to 1.8% of schoolgirls, and 0.03% of schoolboys.[5] Symptomatic UTI will develop in about 1.5% to 2% of children ranging in age from 1 year to 5 years.[39] The risk of bacteriuria developing in girls is 5% to 10% during the school years.[5]

Risk Groups

The children who are at increased risk to have bacteriuria or symptomatic UTI with subsequent renal damage are premature infants discharged from neonatal intensive care units and children with systemic or immunologic disease; urinary tract abnormalities or renal calculi; neurogenic bladder, voiding dysfunction, or constipation; a family history of UTI or anomalies such as reflux; and girls younger than 5 years with a previous history of UTI.

Signs and Symptoms

Neonates with UTI often have bacteremia and may show signs of septicemia including fever, hypothermia, apneic spells, poor skin perfusion, abdominal distention, diarrhea, vomiting, lethargy, irritability, and convulsions. Poor weight gain, palpable kidneys, jaundice, acidemia, and electrolyte imbalance are common. Older infants with UTI may present with feeding problems, a failure to thrive, diarrhea, vomiting, fever, and malodorous urine. A careful history often discloses dribbling, a weak urinary stream, or prolonged

voiding. Abdominal and suprapubic tenderness, pallor, lethargy, and irritability are common physical signs. In older children the classic manifestations of UTI are more commonly observed: enuresis, frequency, dysuria, hesitancy, and suprapubic discomfort in patients with clinical cystitis; malaise, fever, chills, nausea, vomiting, and flank pain occur in those with clinical pyelonephritis.

Physical examination of a child with a possible UTI should always exclude hypertension, an abdominal or flank mass, a palpable bladder, neurologic deficits, abnormal genitalia, and abnormal urinary stream.

The presence of urinary symptoms in the absence of bacteriuria in repeated urine specimens suggests vaginitis, urethritis, masturbation, sexual molestation, the use of bubble baths, pinworms, hypercalciuria, viral cystitis, or, in a patient with hematuria, hemorrhagic cystitis. In adolescent girls, a history of dysuria and vaginal discharge or irritation makes vaginitis or vulvitis more probable.[40]

Sequelae

Urinary Tract Infection

As many as 80% of children with uncomplicated UTI will have recurrences.[1,2] Renal parenchymal infection and renal scarring are well-established complications of UTI in children.[2,11] Parenchymal scarring is found in 10% to 15% of children with this infection.[2] It has been estimated that of these, about 10% will have hypertension and a smaller number renal insufficiency.[2,21] Recently, however, a 27-year follow-up study from Sweden showed that focal renal scarring due to pyelonephritis in a child carried a 23% risk for hypertension, a 10% risk for end-stage renal disease, and a 13% risk for toxemia during pregnancy.[4] Further studies are needed to confirm these alarming findings. Neonatal and infantile UTI, particularly if associated with anatomic defects, results in a high incidence of renal scarring, renal atrophy, and renal insufficiency.[11,41] To reduce the risk of renal damage, the diagnosis and treatment of UTI, particularly in neonates and infants, must be prompt. A high incidence (15% to 50%) of structural urinary tract abnormalities is found in male children with UTI at any age.[42]

Vesicoureteral reflux is found in 30% to 50% of children with UTI but is less common in African Americans.[22] It facilitates the ascent of infected urine to the kidneys.[22] Children with reflux have a much higher incidence (30% to 60%) of pyelonephritic scarring than those without reflux, and more than 90% of children with renal parenchymal scarring have or have had vesicoureteral reflux and a history of UTI.[2] Pyelonephritis and scarring, however, can also occur without vesicoureteral reflux, with transient reflux or with functional ureteral obstruction due to atonic ureters or ureteritis due to infection.[11] Most of the damage to the kidney caused by reflux occurs during infancy and early childhood,[2,21,23] although the development of new scars later in childhood has also been documented.[43] Renal scarring after infantile pyelonephritis is often associated with impaired renal growth with the contralateral kidney showing compensatory hypertrophy.[11] Mild to moderate vesicoureteral reflux (grades 1 to 3) usually decreases or disappears with increasing age [21,44] whereas severe reflux (grades 4 and 5) often persists.[21,22] Vesicoureteral reflux may be familial, and a high prevalence (as much as 45%) is found in asymptomatic siblings of children with reflux.[45,46]

Asymptomatic Bacteriuria

Asymptomatic bacteriuria in children is associated with an increased risk of recurrent symptomatic infections that may result in renal scarring.[2,11] Hypertension or renal insufficiency, however, is unusual.[47] In 20% to 30% of school-aged girls with asymptomatic bacteriuria, radiologic investigation will reveal upper urinary tract damage, vesicoureteral reflux, or both.[47,48] Most of the kidney damage occurs before 5 years of age, however.[48] Most prospective studies of schoolgirls older than 5 years with asymptomatic bacteriuria have failed to demonstrate decreased glomerular filtration rates, impaired renal growth, or progressive parenchymal damage in kidneys that are normal at the start, even if bacteriuria is left untreated.[48-50] Bacteriuria in neonates and infants[5,39] and in boys beyond infancy,[42] however, is associated with a high incidence of urinary tract anatomic abnormalities and necessitates prompt diagnosis and early treatment.

Diagnosis

Proteinuria, hematuria, and pyuria may occur with urinary tract infection but are not diagnostic. Conversely, UTI can occur without pyuria. A positive culture in a urine specimen that is properly obtained is essential for the diagnosis. A positive culture in a specimen obtained by midstream clean catch has 80% diagnostic reliability in a female child and 95% reliability in a male child (less contamination). Two positive cultures in a female patient carry 95% diagnostic reliability.[5,6] In infants and toddlers the confidence level for a single positive culture from a specimen collected in a plastic bag is low.[51,52] Negative cultures of bag specimens are useful, however. Suprapubic aspiration or bladder catheterization is necessary in infants for the prompt and precise diagnosis of infection. In older and cooperative children, a clean, voided midstream specimen is satisfactory. The urine should be processed by a laboratory within 15 minutes after collection or refrigerated at 4°C until plating. The presence of bacteria in unspun or spun urine examined under high-power microscopy or a positive Gram's stain correlates highly with notable bacteriuria.[6]

Several simple and inexpensive techniques have been used for the screening and detection of UTI.[52-54] The Chemstrip Urine Test (Boehringer Mannheim Corporation) is an inexpensive, rapid chemical test that combines the determinations of leukocyte esterase and nitrite concentrations. The leukocyte esterase test detects esterases released from leukocytes that have broken down. The nitrite test detects nitrites that have been produced from dietary nitrates by urinary bacteria. These tests, however, alone or in combination, are not sufficiently sensitive to determine the need for urine culture. False-negative and -positive tests are common, occurring in 15% to 30% of cases, and both tests are characterized by a low positive predictive value.[53-55] A recommended screening method is the "dipslide," which is a slide coated with agar that represents a sensitive and specific alternative to the standard culture.[52,56] The dipslide test can be performed in the office or in a patient's home and used in conjunction with microscopy for the initial diagnosis of UTI, the assessment of antimicrobial effectiveness, and follow-up after treatment.[52]

Contaminated collection of urine specimens, the storage of urine specimens at room temperature, and the presence of

vaginitis are the most common reasons for false-positive urine cultures. False-negative cultures or cultures yielding low colony counts may be caused by diluted urine (afternoon specimen or after taking diuretics), partial treatment with antibiotics, low urinary pH, contamination of the collection container with disinfectants, and complete ureteral obstruction. The growth of mixed bacteria in a urine culture in the absence of a structural urinary tract abnormality usually, though not invariably, indicates a contaminated specimen.

The evaluation, treatment, and prognosis of UTI are related to the site of infection—upper tract versus lower tract. In older children, cystitis is often diagnosed in the presence of dysuria, frequency, and urgency and in the absence of fever or other systemic manifestations, whereas pyelonephritis is diagnosed in the presence of fever—temperature above 38°C—abdominal or flank pain, and systemic upset including pallor, lethargy, irritability, anorexia, and vomiting. Nonspecific tests such as the erythrocyte sedimentation rate and C-reactive protein level in serum have also been used in an attempt to locate the site of infection.[3] Unfortunately, symptoms and tests correlate poorly with the infection site.[10] Other methods used to determine the level of infection have included indirect techniques, such as urinary enzyme activities, serum antibody titers, urinary concentration ability, and antibody-coated bacteria; and direct methods, including ureteral catheterization, bladder washout, or renal biopsy cultures.[1,10,57] Although localizing the level of infection is important, these methods have been used predominantly as tools of research. In clinical practice we do not usually use these tests, with the possible exception of acute-phase reactants. Recently increases in the renal volume of more than 30%, as determined by ultrasonography, were found to indicate upper tract disease.[58,59] Normal ultrasonograms did not exclude upper tract involvement, however. Parenchyma-avid radionuclides such as succimer (formerly dimercaptosuccinic acid [DMSA]) labeled with technetium 99m and technetium Tc 99m gluceptate reveal diminished uptake in areas of focal pyelonephritis,[60-63] and their use appears to be a sensitive and specific approach to determining the level of infection. Further studies are needed to assess the clinical application of ultrasonography and radionuclides in locating infection.

Diagnostic Studies

A radiologic evaluation of the urinary tract in children with UTI is indicated to identify vesicoureteral reflux, obstruction, or other urinary tract abnormalities. In about 50% of children with their first proven case of symptomatic UTI, a structural abnormality will be found.[2,64] Most renal injuries appear to occur in young children,[41,48] and the incidence of structural abnormalities is high in boys,[42] so radiologic evaluation is indicated for the following: a first incident of asymptomatic bacteriuria or UTI in a child younger than 5 years, a first incident of asymptomatic bacteriuria or UTI in any male child, and the recurrence of either of these in any female child. Extensive evaluation, however, is not indicated in a sexually active adolescent girl with recurrent lower tract infections. A family history of UTI or urinary tract abnormalities, an abnormal voiding pattern, poor growth, or hypertension also should prompt a radiologic evaluation of the first incident of UTI.

Voiding cystourethrography (VCUG) and intravenous urography are the time-honored examinations of choice for the initial radiologic evaluation of childhood UTI.[65] The VCUG detects vesicoureteral reflux, affords resolution adequate to grade the severity of the reflux, and provides both anatomic and functional information pertaining to the lower urinary tract. The intravenous urogram is a powerful imaging technique for the upper urinary tract, providing both structural and functional information. The quality of images is related to the adequacy of renal function; thus, neonates with immature renal function and older children with diminished renal function are difficult to evaluate with this tool.

New methods for evaluating renal morphology and function used in recent clinical studies have suggested alternative approaches to the investigation of UTI in childhood.[19,59-61,64,66] The experience, skill, and interest of the interpreting radiologist are important factors in the quality and reliability of the diagnostic evaluation.[19] Although the VCUG provides both direct detection of vesicoureteral reflux and anatomy related to the lower urinary tract, reflux alone can be detected using direct radionuclide voiding cystography. This results in a 50- to 100-fold decrease in gonadal radiation exposure when compared with the conventional VCUG, affords monitoring over a longer period of time, and allows the quantitation of voiding and refluxing events.[67] Anatomic detail, however, is not yet sufficient to grade reflux accurately or to detect anatomic abnormalities that might influence management.

Although the intravenous urogram may remain the single best test for evaluating upper tracts, sonography and radionuclide scintigraphy can be used to evaluate particular aspects of the upper tracts. Sonography is noninvasive, free of ionizing radiation, and capable of providing excellent information regarding renal size, parenchymal texture, size of the collecting system, and anatomy of the bladder.[58,68] Calculi in the urinary tract can also be detected by this tool. Sonography, however, does not detect small focal renal scars and provides only indirect functional information. Thus, abnormal sonograms must often be supplemented by a functional study.

Various radionuclides have been used in the evaluation of the urinary tract.[60,69,70] Parenterally administered technetium Tc99m pentetate (diethylenetriamine-pentaacetic acid [DTPA]) is cleared by glomerular filtration (like inulin) and results in a dynamic radionuclide "intravenous urogram equivalent."[60] The particular strength of this test is in the evaluation of excretory function, which can be quantitated and performed as a "diuretic renogram" when combined with the administration of furosemide. Renal blood flow, closely paralleling global renal function, can be evaluated with iodohippurate sodium I 123 or I 131, which is secreted by the kidney. Again, excretory function is evaluated to a greater extent than is renal parenchyma. Technetium succimer accumulates in functional renal cortex and provides exquisite renal images. It is particularly useful in demonstrating acute pyelonephritis, evaluating focal parenchymal scarring, and assessing solid renal masses versus hypertrophied columns of Bertin.[60,62,70] Technetium succimer, however, delivers a substantial radiation dose to the renal parenchyma and provides no excretory information. Technetium gluceptate is a hybrid agent in that early images using this radionuclide provide information regarding excretion and delayed images show parenchymal detail.

Figure 1 summarizes a reasonable protocol for the radiologic evaluation of UTI in children. The choice of a particular examination, however, depends on the clinical findings, the

facilities available, and the experience and skills of the radiologist. Both VCUG and renal sonography are the initial studies used to determine the next appropriate tests (although some consider the combination of plain abdominal film and renal sonography adequate in children older than 7 years).[64,66] If both tests are normal, no further radiologic evaluation is indicated. In the absence of vesicoureteral reflux, small focal renal scars that may be undetected by ultrasonography are probably of little practical importance in the management of UTI.[68] If reflux is detected, the evaluation of both upper tract structure and function is recommended. If morphologic changes are identified by ultrasonography in the absence of reflux, a search for urinary tract abnormalities such as anatomic obstruction, ureterocele, ectopic kidney, or duplicated system should be carried out. The intravenous urogram serves these purposes well in most instances,

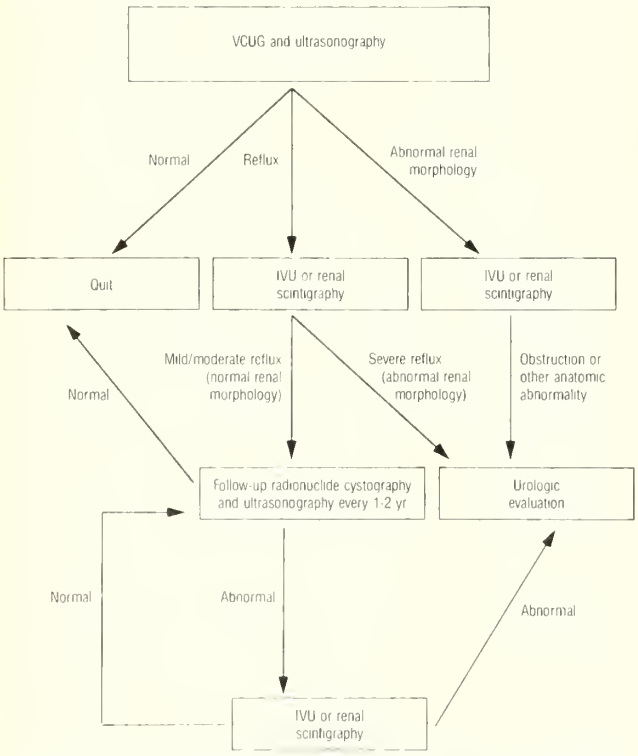

Figure 1.—The diagram shows the protocol for the radiologic evaluation of urinary tract infection in children. IVU = intravenous urography, VCUG = voiding cystourethrography.

but quantitative scintigraphy with ^{99m}Tc-succimer, ^{99m}Tc-pentetate, ^{99m}Tc-gluceptate, or ^{123}I- or ^{131}I-iodohippurate is preferable for neonates and patients in whom poor renal function is anticipated. Moreover, recent studies have suggested that the ^{99m}Tc-succimer scan may be superior to intravenous urography in detecting early renal scars, especially in young children.[71,72] Others, however, think that intravenous urography is still essential for detecting scars.[73] In the presence of moderate or severe vesicoureteral reflux (grades 3 to 5), it is recommended that upper tract evaluations be carried out with a catheter in the bladder because reflux can either simulate or mask renal function.[74]

Follow-up studies of vesicoureteral reflux should be done with radionuclide VCUG to minimize radiation exposure because anatomic detail is not necessary. In cooperative children, a radionuclide VCUG may be obtained without catheterization following intravenous scintigraphy studies. Renal sonography should be done every year or two during follow-up to document normal renal growth.

Transient reflux can be masked or overestimated during an acute UTI, and, thus, the ideal time of the VCUG is four to six weeks after the completion of antimicrobial therapy,[19] although some have suggested such a wait is unnecessary. Certainly if the information is required urgently, the study can be done safely as long as the child is receiving appropriate antibiotics. Similarly, ureteral dilatation on an intravenous urogram (suggesting reflux) is a common transient finding in patients with acute febrile tract infection even in the absence of reflux.[75] Immediate sonography is helpful in an acutely ill child to exclude the combination of infection plus obstruction.

Pelvic radiographs (intravenous urogram or VCUG) taken during the evaluation of UTI should be examined for the presence of lower spine abnormalities. Children with a history suggestive of voiding dysfunction should have a urodynamic evaluation to exclude bladder sphincter dyssynergia.[10] Recently it has been recommended that siblings of patients with known vesicoureteral reflux should have a screening radionuclide VCUG for the early detection of reflux,[45] which is found in as many as 45% of these children[46]; others have argued that such screening is not cost effective.

Screening for Asymptomatic Bacteriuria

Screening for asymptomatic bacteriuria in children is controversial.[76] Although hypertension or renal insufficiency is a rare sequela, bacteriuria in schoolgirls is not an entirely benign condition and may signify an underlying structural abnormality or result in recurrent symptomatic urinary tract infections.[47] The main drawbacks, however, to screening schoolgirls for bacteriuria are as follows:

- A large population must be screened to detect the 1% to 2% with persistent bacteriuria;
- In girls with radiologically demonstrable anatomic abnormalities—0.2% to 0.5% of the school-age population—most of the kidney damage has already occurred before age 5 and may not progress afterwards; and
- There is controversy about the need to treat asymptomatic bacteriuria in schoolgirls.[48,50]

On the other hand, bacteriuria in infancy is often associated with a urinary tract abnormality and may result in intrarenal damage.[3,8] Screening neonates and infants for this disorder is not practical, however, mainly because of the difficulties in obtaining a clean urine specimen in this age group. The only group of children who definitely should be screened—with a semiannual to annual dipslide test or a standard urine culture—are the children at increased risk for bacteriuria and subsequent renal damage (see Risk Groups). The mass screening of children for bacteriuria is not recommended at this time.

Management

The approach to the treatment of UTI in children is based on clinical severity, site of infection, age, the presence of structural abnormalities, and the patient's compliance.[3,5,77] Immediate treatment, especially in infants and young children with vesicoureteral reflux or other urinary tract abnormalities, is important because delay increases the risk of renal parenchymal scarring.[11] The antibiotics used in the treatment of UTI in children are listed in Table I.

Symptomatic UTI in neonates is frequently associated with sepsis and substantial mortality and, therefore, after complete studies for sepsis, should be treated with parenteral antibiotics for seven to ten days, usually using a combination of ampicillin and an aminoglycoside.[3]

Young infants with UTI, children with clinical evidence of acute pyelonephritis, and children with upper tract infection associated with urologic abnormalities or surgical procedures often require hospital admission and intravenous antibiotic therapy. Therapy can be initiated with a combination of an aminoglycoside and ampicillin or an aminoglycoside and cephalosporin.[3,5] The extended-spectrum penicillins such as piperacillin or azlocillin are especially active against *Pseudomonas* species and have been used successfully as single-agent therapy for severe and complicated UTI.[5] The recently introduced aminoquinolones are not generally recommended for children and should be reserved for infections with multiply resistant *P aeruginosa*.[77] In the presence of renal insufficiency, dosages of antibiotics excreted in the urine must be modified.

TABLE 1.—*Antibiotics Used in the Treatment of Urinary Tract Infection in Children*

Antibiotic	*Route of Administration*	*Dosage, mg/kg/day*
Amikacin	Parenteral	15 every 8 hr 7.5 every 12 hr (neonate)
Amoxicillin	Oral, parenteral	20-50 every 8 hr
Ampicillin	Oral, parenteral	50-100 every 6 hr
Cefaclor	Oral	20-40 every 8 hr
Cefazolin sodium	Parenteral	100-150 every 6-8 hr
Cefotaxime sodium	Parenteral	150 every 6-8 hr
Ceftazidime	Parenteral	150 every 8 hr
Ceftriaxone sodium	Parenteral	100 every 12-24 hr
Cephalexin	Oral	50 every 8 hr
Mezlocillin	Parenteral	100-150 every 4-6 hr
Nitrofurantoin	Oral	5-7 every 6 hr
Piperacillin sodium	Parenteral	100-150 every 4-6 hr
Sulfisoxazole acetyl	Oral	120-150 every 6 hr
Ticarcillin	Parenteral	200-300 every 6 hr
Tobramycin, gentamicin sulfate	Parenteral	5-7.5 every 8 hr
Trimethoprim (TMP) and sulfamethoxazole (SMZ)	Oral	8-10 TMP, 40-50 SMZ every 12 hr

In children with symptomatic lower UTI with or without reflux, oral therapy may be initiated with amoxicillin, ampicillin, sulfisoxazole acetyl, a combination drug containing trimethoprim and sulfamethoxazole, nitrofurantoin, or cephalosporins.

Controversy exists about the need for antibiotic treatment of asymptomatic bacteriuria.[76,77] The following objections have been raised:

- Treatment only reduces the duration of bacteriuria but has no effect on the emergence of symptoms, the clearance of vesicoureteral reflux, kidney function, kidney growth, or the progression of kidney scars[48,50];
- Short-term therapy may eradicate organisms of low virulence, but may precipitate acute pyelonephritis following recolonization by virulent organisms[78,79]; and
- Side effects may be associated with long-term antibiotic administration.

We treat children with asymptomatic bacteriuria if they are younger than 5 years, have a urinary tract structural abnormality, or if symptomatic UTI develops. Uncomplicated UTI and asymptomatic bacteriuria usually respond to treatment within 24 to 48 hours as evidenced by clinical improvement, a negative Gram's stain of the urine specimen, and sterile urine. If the patient responds to therapy adequately, in vitro susceptibility reports can be ignored because urinary antibiotic levels often markedly exceed the serum levels simulated by disc antibiotic sensitivity testing. A failure of response suggests noncompliance, poor absorption of the drug, bacterial resistance, improper dosage, or an underlying structural defect indicating the need for prompt radiologic evaluation.

Uncomplicated UTI or asymptomatic bacteriuria is usually treated for seven to ten days. The successful treatment of uncomplicated UTI in children has been reported with a three-day course of various antibiotics,[80] a single dose of oral amoxicillin (50 mg per kg),[81,82] or a single parenteral dose of gentamicin sulfate (5 mg per kg) or netilmicin sulfate (4.5 mg per kg).[83,84] Cure and recurrence rates in children treated with short-course therapy were comparable in some studies to those achieved with conventional seven- to ten-day treatment. The advantages of short-term therapy are better compliance, fewer side effects, cost savings, and less likelihood of altering fecal flora or selecting for bacterial resistance. The use of short-course therapy for UTI in children is still controversial, however.[85,86] Moffat and co-workers critically reviewed 14 published trials of short-course (<4 days) versus conventional (7 to 10 days) therapy and found that there was insufficient evidence to support the use of short-course therapy because of inadequate sample size and study methods. Until further data are available, this method of treatment should be reserved for selected patients with asymptomatic bacteriuria and girls older than 5 with clinical findings of lower tract infection, a documented normal genitourinary tract, and poor compliance.

A urine culture by dipslide or calibrated loop should be done three to seven days after the completion of therapy to exclude relapse. The importance of a follow-up culture cannot be overemphasized. Relapses usually occur within a week of completing therapy, are caused by the same bacteria, and often signify upper tract infection.[6] In contrast, the recurrence of UTI occurs from weeks to months after an infection and is commonly caused by different species of bacteria.[6] In every child with documented bacteriuria or UTI, two to three urine cultures per year should be obtained to detect recurrences. Usually three documented infections in a year indicate the need for prophylactic therapy. Both trimethoprim-sulfamethoxazole (10 mg per kg per day of sulfamethoxazole) given nightly or on alternate nights and nitrofurantoin (1 to 2 mg per kg per day) given nightly are highly effective in preventing recurrences and have few side effects.[3,77,87] Antibiotic prophylaxis may be continued for six months to two years. In selected patients with persistent vesicoureteral reflux, prophylaxis may need to be extended for several years because of the potential risk of new scar formation.[43] Prophylaxis is recommended for all children younger than 5 with vesicoureteral reflux or other urinary tract abnormalities. Some recommend that children who undergo catheterization of the urethra for any reason should receive full-dose prophylactic antibiotic therapy for 48 hours from the time of catheterization.[77]

Mild to moderate reflux (grades 1 to 3) usually disappears

with increasing age. Surgical intervention is not indicated if urine cultures are repeatedly sterile, long-term prophylactic therapy can be maintained, and sonograms every one to two years document adequate renal growth.[2,44] Double voiding and the avoidance of constipation are recommended preventive measures against infection. Patients should be referred to an experienced urologist for possible ureteral reimplantation if there is severe vesicoureteral reflux, increased reflux, uncontrolled infection, breakthrough infections, progressive scarring, renal growth arrest, or medical noncompliance. Surgical intervention may not decrease the incidence of UTI, but may reduce upper tract involvement.[1] Controversy exists whether reimplantation has a beneficial effect in preserving renal function, improving renal growth, and altering the course of chronic renal deterioration, especially when renal function is already decreased.[21,23] A recent five-year follow-up study of surgical versus medical treatment of severe vesicoureteral reflux in children reported no difference in the incidence of breakthrough urinary infections, renal tubular function, renal growth, the progression of existing renal scars, or new scar formation.[88] The submucosal administration of various substances (Teflon, bovine collagen) has been used recently as an alternative to ureteral reimplantation.[89] Concern remains, however, about the biocompatibility of these materials and about their suitability for the long-term prevention of vesicoureteral reflux.[89] Patients with obstruction or voiding dysfunction, such as neurogenic bladder or dyssynergia, should also be referred to a urologist.

There is no evidence that urethral dilatation, meatotomy, or urethrostomy reduces the incidence of UTI. Good hygiene including front-to-back wiping of the anus has been recommended. The use of shampoos, bubble bath, or other chemical irritants should be avoided. Constipation, often diagnosed only after a careful history, should be corrected.

Urinary tract infection complicated by neurogenic bladder, obstruction, or indwelling catheters responds poorly to antibiotic therapy unless the complication is corrected. Intermittent bladder catheterization has dramatically reduced infectious complications of neurogenic bladder.[90]

Summary

The early diagnosis and prompt treatment of urinary tract infection, especially in infants and young children, are of crucial importance. One must be aware of the nonspecific manifestations of UTI early in life when most of the kidney damage due to infection occurs. The diagnosis of UTI in questionable cases, especially in infants, should be verified by suprapubic aspiration or sterile bladder catheterization. The diagnosis demands prompt radiologic evaluation of the urinary tract in all male children, all children younger than 5 years, all patients with voiding dysfunction, and school-aged girls with recurrent UTI. The VCUG coupled with renal sonography remains the essential initial examination in children with UTI; the results of these tests determine whether intravenous urography or renal scintigraphy is the next appropriate test. Children with vesicoureteral reflux or with recurrent UTIs should receive prophylactic antibiotics and should be followed closely to prevent the development of renal parenchymal scars. In certain high-risk groups, asymptomatic bacteriuria may signify an underlying urinary tract abnormality and should be evaluated and treated accordingly. Further studies are needed to investigate the role of short-course antibiotic therapy in the management of UTI in children.

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Epitomes

Important Advances in Clinical Medicine

Anesthesiology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in anesthesiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Transesophageal Echocardiography

TRANSESOPHAGEAL ECHOCARDIOGRAPHY offers a new perspective on the heart. With the introduction of smaller, more sophisticated transducers and the addition of color-flow Doppler and biplanar imaging, transesophageal echocardiography has become widely accepted as a low-risk method for the rapid, accurate examination of myocardial function, valvular disease, and aortic anatomy.

In skilled hands, transesophageal echocardiography is considered safe, with a low (< 1%) incidence of complications such as arrhythmias, hypotension, bronchospasm, and aspiration. The most catastrophic complication, esophageal rupture, is extremely rare and has been reported only in patients with esophageal disease or carcinoma; transesophageal echocardiography is contraindicated in these cases. The procedure is also proscribed in nonfasting patients and in those with severe bleeding diathesis.

Although transesophageal and transthoracic imaging are based on the principles of ultrasonography, transesophageal echocardiography is superior in most cases. The retrocardiac approach produces higher resolution images, avoids tissues, improves ultrasound transmission, and avoids the necessity of interrupting a thoracic procedure for imaging. Finally, the location affords excellent visualization of both valvular prostheses and aortic anatomy. In fact, because it does not require a contrast medium and can be done at the bedside, transesophageal echocardiography may be preferable to computed tomography and angiography for evaluating aortic dissection in centers with adequate facilities and experienced staffs.

In the past several years, anesthesiologic and critical care uses for transesophageal echocardiography have expanded rapidly. Preoperatively, it is useful for evaluating baseline cardiac performance and valvular anatomy and can define intracardiac vegetations, masses, and thrombi with exquisite detail. Postoperatively, it can complement other monitoring methods in the intensive care unit to follow hemodynamics and cardiac function.

Intraoperative transesophageal imaging is now routinely done during cardiac and high-risk operations in many centers. Transesophageal echocardiography can detect myocardial ischemia at its earliest observable stage, when ventricular relaxation becomes impaired and regional wall motion abnormalities occur. These changes are seen before electrocardiographic ST segment shifts and provide the opportunity to promptly recognize and treat intraoperative ischemia. In addition, pulsed-wave Doppler examination of pulmonary venous flow may help predict changes in pulmonary capillary wedge pressure and associated volume shifts. Finally, transesophageal echocardiography is often invaluable for the intraoperative assessment of valvular insufficiency, repair, and replacement. All of these benefits depend on physicians' experience and procedural skill. Many transesophageal echocardiography determinants are semiquantitative in nature, and thorough training in echocardiography is essential to avoid misinterpretations.

Several recent advances are important to note. Biplanar transesophageal echocardiography probes with two orthogonally arranged crystal arrays were introduced several years ago and allow both transverse and longitudinal cross-sectional imaging of the heart. In the near future, multiplanar probes with electronically adjustable transducer angulation will become generally available. These will permit visualizing almost any imaging plane and will compensate for a lack of probe flexibility within the esophagus.

Echocardiographic contrast material for intravascular and intracardiac administration is now being commercially produced. This fluid is extremely "echo-dense" and reflects ultrasound waves efficiently, even at relatively low concentrations. Echocardiographic contrast can be administered to the right or left ventricle to enhance endocardial border definition and can also be infused intraoperatively into coronary arteries or bypass grafts. In the latter cases, the contrast is carried into the myocardium, which then becomes noticeably brighter on echocardiographic imaging. This is a promising new technique to assess the patency of coronary bypass grafts before the operation is completed and the chest is closed.

A development called acoustic quantification is also now available. With this technology, endocardial borders in a region of interest are automatically defined and enhanced, and real-time changes in left or right ventricular cross-sectional areas can be instantaneously calculated and displayed. With advanced instruments, ultrasonic tissue characteristics of the

myocardium can also be studied. This may prove useful in assessing cardiac performance, intrinsic myocardial abnormalities, and, indirectly, ventricular stroke volumes. The combination of multiplanar imaging and acoustic quantification could ultimately lead to clinically practical three-dimensional imaging of the heart.

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New Applications of Propofol

SINCE ITS INTRODUCTION IN 1989, propofol has rapidly become popular for inducing and maintaining anesthesia. Propofol has two unusual characteristics that account for this popularity. On the pharmacokinetic side, propofol has a rapid clearance, 1.5 to 2 liters per minute, which exceeds hepatic blood flow. Propofol is also highly fat soluble and sequesters in fat following long infusions. These pharmacokinetic properties result in a rapid decrease in propofol concentration following continuous infusions, regardless of the infusion duration. On the pharmacodynamic side, subhypnotic doses of propofol do not cloud consciousness. The net effect is that patients recover rapidly at the end of long infusions.

The US Food and Drug Administration this year approved the use of propofol for "monitored anesthesia care sedation." In this situation, propofol, when compared with midazolam hydrochloride, allows a more rapid titration to the level of sedation and a faster return of clearheadedness. The more rapid blood-brain equilibration of propofol (1 to 2 minutes) compared with midazolam (2 to 4 minutes) means that the level of consciousness can be more rapidly decreased with propofol in anticipation of an imminent noxious stimulus. Once the stimulus is over, the patient can be returned to a lighter level of sedation more rapidly with propofol than with midazolam. This is particularly important if the patient must occasionally interact with the surgeon. Older patients sometimes become excited with the use of midazolam, but not with propofol. Like midazolam, propofol is a potent ventilatory depressant, particularly when combined with opioids. Therefore, the use of propofol for sedation is recommended only when administered by anesthesiologists or other personnel who have been trained in acute airway management.

Propofol is also being investigated for the long-term sedation of intubated patients in intensive care units. The current standard in many hospitals is a continuous infusion of midazolam and an opioid. This regimen results in a substantial accumulation of midazolam and prolonged sedation when the infusion is terminated. The high clearance of propofol permits a rapid decrease in propofol concentrations, even after infusions of one to two weeks. This allows for awakening a patient at regular intervals for the frequent assessment of neurologic status. Provided that the patient has adequate cardiac filling pressures and that judicious titration is used to achieve the appropriate level of sedation, propofol used for sedation in the intensive care unit is usually not associated with the hypotension that accompanies the induction of anesthesia in an operating room. Additional benefits of using propofol in critically ill patients are a decreased metabolic oxygen requirement, with a concomitant increase in mixed venous oxygen saturation, and little need for vasodilators or negative inotropes in hyperdynamic patients. As propofol has no intrinsic analgesic properties, it is helpful to give a small amount of an opioid concurrently. This reduces the amount of propofol required to produce the desired level of sedation.

Propofol also appears to have antiemetic properties. Many of the initial clinical studies documented a low incidence of nausea and vomiting following propofol anesthesia. In several recent studies, propofol was found to be effective in treating chemotherapy-induced emesis. The propofol concentrations that appear effective in treating nausea are well below those associated with sedation.

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'Do-Not-Resuscitate' Orders in Operating Rooms

PATIENTS WITH "do-not-resuscitate" (DNR) orders may come to operating rooms for procedures to palliate symptoms. They also may need operations to treat lesions related or unrelated to the disease that led to the DNR decision. How is the DNR status to be handled by operating room personnel? This is an important question because common interventions in operating rooms could be labeled resuscitation in other settings. It may be difficult to separate resuscitation required to reverse acute anesthesia- or surgery-related problems from that needed to reverse events caused by the underlying disease.

At least four options exist for dealing with DNR orders perioperatively:

- Allow the preoperative DNR order to stand, but suspend the DNR order during and soon after the operative period. In this instance DNR plans can be reinstituted when the patient has recovered from the acute effects of anesthesia;
- Life-sustaining measures instituted intraoperatively can be withdrawn postoperatively. For example, if a patient has become ventilator dependent, an agreement to discontinue such treatment can be documented preoperatively;
- Provide all resuscitative measures short of cardiac massage;
- Suspend DNR orders but reinstate them intraoperatively if cardiac arrest occurs related to the disease that led to the DNR orders, such as hypovolemic shock during a portacaval shunt in a patient with advanced cirrhosis and encephalopathy.

In recent lively and thoughtful debates about DNR orders in patients requiring surgical treatment, each of the above options or blends of these options has been proposed. Federal law (Patient Self-Determination Act of 1990) requires that patients entering institutions receiving Medicare or Medicaid funds must be advised of their right to issue advanced

directives. All hospitals seeking accreditation from the Joint Commission on Accreditation of Healthcare Organizations must have DNR policies. Policies should include the management of DNR orders when surgery and anesthesia are required.

Communication among surgical professionals, the primary care team, and the patient and family about DNR orders in the perioperative period must be clear and open. The goal is to remove ambiguity about the perioperative care of patients to the greatest possible extent. This will require patience and time. Both must be provided.

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Novel Approaches to the Treatment of Neuropathic Pain

INJURY OR DISEASE of the central or peripheral nervous system causes some of the most agonizing and intractable chronic pain problems. Pain can result from nervous system injury caused by direct trauma (brachial plexus avulsion, phantom limb pain), ischemia (thalamic syndrome), infection (tabes dorsalis, postherpetic neuralgia), metabolic derangements (diabetic neuropathy), or tumor invasion (lumbosacral plexopathy). Patients with these syndromes may describe sensations of intolerable burning, searing, crushing, electric shocks, pins and needles, or tearing of the flesh and often suffer serious disability as a result. Suicide is an unusual but well-described complication of neuropathic pain.

Anesthesiologists are frequently requested to consult on patients with neuropathic pain with the hope that a patient may respond favorably to a neural blockade technique. Unfortunately, even when there is an initial favorable response to a block, the results may not be long-lasting, and medical management often assumes an important role. The treatment of neuropathic pain is complicated by the fact that routine analgesics such as nonsteroidal anti-inflammatory drugs and opiates may be ineffective. In fact, a lack of pain relief from standard doses of opiates may point to the diagnosis of neuropathic pain. Fortunately other types of drugs not normally classified as analgesics are often effective for the relief of neuropathic pain. These include tricyclic antidepressants, anticonvulsants, parenteral administration of topical anesthetics, and α-adrenergic antagonists.

It is now well established that tricyclic antidepressants relieve pain in a variety of neuropathic conditions. This analgesic action of the tricyclics is independent of any antidepressant effect. Amitriptyline hydrochloride has been the most extensively studied and most widely used tricyclic for the relief of neuropathic pain, but many other tricyclics have proved to be effective, including nortriptyline hydrochloride, imipramine hydrochloride, and desipramine hydrochloride. Toxicity is rarely a problem in the dose ranges normally required for analgesia, and tricyclics do not produce euphoria or tolerance so that abuse potential is low. The mechanism of analgesia from the tricyclic compounds is thought to be an inhibition of the uptake of biogenic amines, such as serotonin and norepinephrine, which are known to inhibit pain-transmitting neurons.

Anticonvulsant drugs may also be useful for the treatment of neuropathic pain, particularly when a patient reports a paroxysmal lancinating or "electric shock" component to the pain. Experimental evidence suggests that injured nerves may develop hyperexcitability and spontaneous ectopic activity. Thus, paroxysmal neuralgic pain resembles epilepsy in certain respects, and in these patients antiepileptic drugs may provide pain relief. Carbamazepine is now the treatment of choice for trigeminal neuralgia, and more recently clonazepam and sodium valproate have been shown to be useful for the treatment of various lancinating pains, as may occur in postherpetic neuralgia, tabes dorsalis, phantom limb pain, diabetic neuropathy, and the thalamic syndrome.

The intravenous infusion of lidocaine has been shown to suppress spontaneous activity in neuromas and to reduce pain in diabetic neuropathy and other neuropathic conditions. Intravenous lidocaine infusion may eventually prove to be a useful test to identify a neuropathic component to a chronic pain syndrome. These observations have stimulated interest in the use of the oral antiarrhythmic and lidocaine congener mexiletine hydrochloride, which was recently shown to reduce neuropathic pain in patients in whom alternative medical regimens had been unsuccessful. In particular, patients with a "burning" component to the pain seemed to benefit from oral mexiletine, and side effects were minimal. The mechanism of action of these drugs is unclear, but may involve alterations in spinal cord processing, rather than by peripheral axonal or receptor blockade.

Neuropathic pains are often maintained or augmented by efferent activity in the sympathetic nervous system, as occurs in the reflex sympathetic dystrophy syndrome. This condition has traditionally been diagnosed and treated by repeated regional anesthetic blocks of the appropriate sympathetic ganglia. Recent experimental evidence has suggested that sympathetically maintained pains are mediated largely through α-adrenergic mechanisms. The intravenous infusion of phentolamine mesylate has been described as a reliable, specific, and easy-to-do diagnostic test for sympathetically maintained pain. For patients who respond to phentolamine infusion, daily treatment with oral phenoxybenzamine hydrochloride or other α-adrenergic antagonists may permanently eradicate sympathetically mediated components of the pain. Side effects such as orthostatic hypotension may limit therapy, however.

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Postoperative Pain

THE SIDE EFFECTS OF postoperative pain management have long been a focus of attention. Concern has now shifted to the possible morbidity of inadequate therapy; indeed, there is a growing body of evidence that postoperative pain may have harmful physiologic and psychological effects. Specifically, pain may adversely affect respiratory function, contribute to

the development of a stress response, increase cardiac morbidity, and prolong hospital stays.

New analgesic agents have led to improvements in acute pain management. The recent approval of ketorolac tromethamine, a potent nonsteroidal anti-inflammatory agent, has provided physicians with a nonopioid alternative for the treatment of mild to moderate pain and a useful adjunct to decrease the opiate requirement of moderate to severe pain. Possible advantages include the lack of sedation, respiratory depression, or disturbance of bowel and bladder function. Unfortunately, the use of ketorolac may be associated with serious side effects, including gastrointestinal ulceration, platelet dysfunction, and nephrotoxicity. Patients who are hypovolemic or have preexisting renal insufficiency may be particularly vulnerable to the nephrotoxicity.

Even more important than the introduction of new analgesic agents has been the increased use of regional anesthetic techniques and the development of better methods of drug delivery, particularly patient-controlled analgesia and the spinal administration of narcotics. Although narcotics (fentanyl citrate) may also be administered transdermally, this route is not well suited for the initial treatment of acute postoperative pain because 12 to 24 hours are required to reach a steady state. Transdermal administration, however, appears to have a useful role in the treatment of patients who, after several days, still cannot take anything orally and have relatively stable pain.

Numerous surveys have documented that scheduled or patient-requested, intermittent, intramuscular administration of narcotics fails to control postoperative pain. Patient-controlled analgesia effectively circumvents problems of variable absorption and delays. When in pain, the patient depresses a button, causing the delivery of a fixed intravenous dose from an infusion pump. The physician sets both the dose of drug delivered by the machine and the "lockout" interval, which is the time after a dose during which a second dose cannot be delivered by the machine. The "lockout" should be of sufficient duration to allow the patient to obtain near-peak effect from the dose already received, thereby safeguarding against overdosage due to cumulative effects. Along with administration based on patient demand, a low-dose continuous or basal infusion can be provided. The theory is that supplementation with a basal infusion should provide more effective pain control and encourage uninterrupted sleep; unfortunately, although the data are somewhat equivocal, they do not appear to confirm these benefits. In addition, the inclusion of a basal infusion may decrease the relative safety of the technique. Most studies document improved control of pain with patient-controlled analgesia. Moreover, patient acceptance is exceptionally high; in fact, in one controlled study, the use of patient-controlled analgesia resulted in greater patient satisfaction than the epidural administration of morphine sulfate, even though patients receiving epidural morphine had better analgesia.

Unlike the administration of systemic narcotics, the spinal administration of opiates can produce profound analgesia without a significant depression of the sensorium. Selective spinal analgesia can be achieved using either epidural or intrathecal opioid administration, but the use of an epidural catheter technique permits continuous or repeated injections to provide analgesia for prolonged periods and allows for the substitution or addition of local anesthetics. Although clinical management is more complex when local anesthetics are combined with spinal opioids, the combination can increase analgesia, delay tachyphylaxis, and reduce the side effects that occur when either technique is used alone.

The importance of aggressive postoperative pain management has been underscored by the recent publication of clinical practice guidelines for acute pain management by the Agency for Health Care Policy and Research. The guidelines stress a collaborative interdisciplinary approach; an individualized plan developed preoperatively; assessment and frequent reassessment of the patient's pain; the use of both drug and nondrug therapies; and a formal institutional approach, including incorporating a quality assurance program.

The effective control of postoperative pain is important and necessary not only for patient comfort but also for rapid recovery and optimal results. The effectiveness of newer methods such as patient-controlled analgesia and intraspinal techniques and the availability of newer, more potent, nonsteroidal anti-inflammatory drugs permit far more effective management of postoperative pain than with traditional intramuscular therapy.

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Perioperative Myocardial Ischemia

DESPITE RECENT ADVANCES in the diagnosis and treatment of coronary artery disease, the incidence of perioperative cardiac morbidity remains high. As a result, considerable research has been devoted to investigating perioperative myocardial ischemia as a possible reversible predictor of adverse surgical consequences.

Intraoperative electrocardiographic changes consistent with myocardial ischemia occur in 18% to 74% of patients with coronary artery disease who are having noncardiac operations. A recent study shows that ST segment changes occur laterally (V_4, V_5) and have a variable duration. Although intraoperative ischemia can be precipitated by increases in myocardial oxygen demand due to tachycardia and hypertension, 50% or more of the ischemic episodes may be unrelated to increases in indices of oxygen demand, suggesting that a primary decrease in the oxygen supply may be an important cause.

Although a previous study suggested that the occurrence of ischemia in the pre-bypass period in patients undergoing coronary artery bypass grafting may increase the risk of postoperative myocardial infarction, more recent studies show that a chronic pattern of ischemia exists preoperatively in patients having coronary artery bypass grafting as well as those having noncardiac surgical procedures. Furthermore, the intraoperative pattern of ischemia is no worse than the preoperative pattern, implying that anesthesia and surgery may not be as stressful as previously assumed and that the intraoperative pattern may simply recapitulate the ongoing preoperative pattern.

Finally, it is now established that postoperative ischemia is even more prevalent than ischemia occurring before or during an operation and is the most important predictor of

adverse cardiac events in high-risk patients undergoing noncardiac operations. In fact, postoperative myocardial ischemia as detected by Holter electrocardiographic monitoring confers a 9.2-fold increase in the odds of a cardiac event. No other clinical, historical, or perioperative variable was associated independently with adverse cardiac results, including the cardiac risk index, a history of previous myocardial infarction or congestive heart failure, or the occurrence of ischemia before or during an operation. Accordingly, increased attention and resources should be focused on the postoperative period. Clinical trials of perioperative antiischemic therapies are currently under way. The results from these trials will determine whether the incidence of perioperative cardiac morbidity can be reduced by the prevention of postoperative ischemia.

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Sedating Patients in Intensive Care Units

ANXIETY, SLEEP DEPRIVATION, and pain are extremely common problems in patients in intensive care units and can lead to delusions, delirium, or psychosis. The neuroendocrine stress responses often associated with noxious conditions can produce deleterious hemodynamic, metabolic, nutritional, and immunologic changes. Inadequate control of any of these problems frequently results in unnecessarily large doses of sedatives. Coughing with an endotracheal tube and fighting the ventilator complicate the management of patients on ventilatory support. Asynchrony between spontaneous ventilatory efforts and mechanical breaths predisposes patients to pulmonary barotrauma, interferes with alveolar gas exchange, and increases the work of breathing. Neuromuscular paralysis for the control of inappropriate (central) hyperventilation mandates that sedation also provide amnesia.

Older sedation practices relied primarily on intermittent intravenous doses of morphine sulfate or meperidine hydrochloride. Diazepam or pentobarbital was given when amnesia or hypnosis was required. Unfortunately, boluses of these long-acting agents often caused serious circulatory and respiratory depression, and the high doses of opiates decreased gastrointestinal motility and prolonged ileus.

Midazolam hydrochloride, a short-acting benzodiazepine, has a pharmacokinetic profile that readily allows titration to effect when given by continuous intravenous infusion. Loading is best achieved by 0.5-mg increments followed by an infusion of 0.015 to 0.2 mg per kg per hour. Respiratory or circulatory depression is generally minimal, and even after prolonged infusions its effects usually dissipate within two hours after the infusion is stopped. The latter facilitates a rapid weaning from mechanical ventilation and neurologic evaluation. Withdrawal symptoms are uncommon, but tolerance may develop in some patients.

Supplementing midazolam is important whenever a patient has substantial pain, is on a ventilator, or tolerance develops. A concomitant infusion of an opioid or ketamine hydrochloride augments the sedation, provides analgesia, and reduces drug requirements. Adding fentanyl citrate, 0.5 to 2 μg per kg per hour, sufentanil citrate, 0.05 to 0.2 μg per kg per hour, or alfentanil hydrochloride, 5 to 20 μg per kg per hour, can produce excellent analgesia and reduces midazolam requirements. Alternatively, ketamine, 0.15 to 0.5 mg per kg per hour, can also provide powerful analgesia. Unlike opioids, ketamine is a bronchodilator and mild respiratory stimulant. Psychotomimetic reactions, such as hallucination and nightmares, are uncommon when ketamine is combined with a benzodiazepine.

Propofol, a short-acting intravenous anesthetic with a rapid onset and termination, is an excellent sedative at low doses—1 to 6 mg per kg per hour. Dose-dependent respiratory depression and hypotension can be observed after administering a bolus but are generally minimal when propofol is given by infusion at this dose range. Propofol's principal advantage is that its effects usually dissipate within 15 to 20 minutes after the infusion is stopped. Withdrawal symptoms have been reported following prolonged propofol infusion.

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Perioperative Temperature Control

HUMANS NORMALLY MAINTAIN a core body temperature near 37°C. This temperature is maintained because deviations of only a few tenths of a degree trigger thermoregulatory responses, including vasoconstriction, shivering, active vasodilation, and sweating. General anesthetics profoundly impair normal thermoregulatory processing. For example, the core temperature triggering vasoconstriction is decreased from about 37°C to about 34°C by halothane, nitrous oxide and fentanyl citrate, nitrous oxide and propofol, and isoflurane. The exact triggering threshold depends on the anesthetic type and dose, but is similar in infants, children, and adults. In contrast, the core temperature triggering sweating and active vasodilation is increased about a degree by surgical concentrations of isoflurane and enflurane. The interthreshold range (core temperature not triggering thermoregulatory responses) thus is increased by general anesthesia from about 0.6°C to about 4°C.

Most patients become hypothermic during surgical procedures, and hypothermia usually develops in three distinct phases. During the first hour, the core temperature decreases about 1°C. Surprisingly, undressing patients in a cold room and washing their skin with fluid that is subsequently allowed to evaporate contributes little to the hypothermia. Anesthetic-induced vasodilation only minimally increases heat loss from the skin surface. Similarly, inducing anesthesia only minimally reduces metabolic heat production. Core hypothermia actually results because vasodilation allows heat in warm core tissues to escape into the cooler peripheral thermal compartment. This reduces the core temperature, increases the peripheral temperature, and leaves the body heat content unchanged.

Redistribution hypothermia is followed by a slow linear decrease in the core temperature, lasting two to three hours. This linear decrease apparently results simply from heat loss exceeding metabolic heat production. Finally, after three to four hours of anesthesia, the core temperature becomes constant and does not decrease further even during prolonged surgery.

Intraoperative hypothermia is most common in infants and children because of a high surface area-to-mass ratio and in elderly patients because thermoregulatory responses are impaired. Mild hypothermia—2°C to 3°C below normal—protects against hypoxia, ischemia, and malignant hyperthermia. Consequently, hypothermia is appropriate in patients in whom ischemia can be expected, such as during carotid and neurosurgical procedures. Conversely, hypothermia decreases drug metabolism, impairs coagulation, decreases resistance to wound infections, and provokes postanesthetic shivering. Most patients should therefore be maintained at normal temperature. Hypothermia is best treated using a high ambient temperature or forced-air warming. Circulating-water warmers placed over patients substantially decrease heat loss but are relatively ineffective when positioned under patients. Warming intravenous fluids is critical when large volumes are administered. Airway heating and humidification transfer little heat and are not worth the expense in adult patients.

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Postoperative Apnea Syndrome in Premature Infants

THE PREDISPOSITION OF preterm infants to episodes of apnea in the postoperative period has been recognized for a decade. What progress has been achieved during this time in our understanding of the etiology of this problem, and how should these patients be managed?

Infants younger than 45 weeks of conceptual age (conceptual age is the sum of gestational age and postnatal age) are more likely to be affected. Although conceptual age is a significant predictor of problems, there is also a suggestion that infants who were born at an early gestational age are at a further increased risk. In addition, a number of other predisposing factors have become recognized. These include anemia, a history of the respiratory distress syndrome, persistent chronic respiratory disease, and previous apneic episodes. Although a history of apnea is clearly important, infants with no previous episodes of apnea may also be at risk to suffer an apneic episode in the postoperative period. Apnea usually occurs within the first few hours after the operation, but in smaller infants may occur much later. The apnea is central in origin in most instances, but obstructive apnea may also occur. Apnea is more likely to occur after general anesthesia, but life-threatening apnea may rarely occur even if only regional analgesia has been used.

Current recommendations are that the management of preterm infants generally should include hospital admission and careful postoperative monitoring of all surgical patients who are younger than 50 weeks of postconceptual age. Such infants should be treated in hospitals that have a neonatal service and a neonatal intensive care unit. After the operation they should be monitored with an apnea alarm in an area under close nursing supervision for 12 to 24 hours or more, depending on their history. The presence of anemia, chronic respiratory disease, or persistent episodes of apnea are indications to admit older infants. The use of spinal or caudal anesthesia may be advantageous, especially in those infants with a previous history of prolonged ventilatory support.

Intravenous caffeine therapy, 10 mg per kg, given at the induction of anesthesia has been suggested to reduce the danger of postoperative apnea, but close postoperative observation is still recommended. At present, the use of caffeine therapy is not common. The influence of theophylline therapy on the danger of postoperative apnea has not been fully studied.

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Autologous Blood Transfusion Therapy

THE PROBABILITY THAT homologous blood transfusions will transmit infectious diseases has decreased with thorough blood donor screening and sophisticated laboratory testing. The risk of contracting a potentially lethal infection nonetheless remains finite (1 in about 40,000 units for the human immunodeficiency virus [HIV]). Autologous blood transfusion is the safest alternative for some patients having surgical procedures. In California, whenever there is a reasonable possibility that a patient having a procedure will require a blood transfusion, the patient must be informed of the risks and benefits of the various options for managing transfusion therapy.

Few surgical procedures are commonly associated with a critical volume of blood loss that warrants transfusion therapy. Patient-specific factors such as size, cardiovascular status, pulmonary function, and hematologic profile are important in decisions relating to transfusion. Autologous blood for transfusion in the perioperative period may be obtained by preoperative autologous donation, normovolemic hemodilution, intraoperative blood salvage, or postoperative blood salvage. Alone or in combination, these can decrease or eliminate the need for homologous blood transfusion.

As many as four to five autologous units can be safely donated preoperatively during the six-week shelf life of erythrocytes collected in adenine-supplemented preservatives. The plasma can be freshly frozen. The hematocrits of autologous donors are monitored, and treatment with oral iron is routine. The value and role of recombinant human erythropoietin remain under investigation. Because the morbidity of donation is predominantly related to vasovagal reactions, clinically adverse hemodynamic sequelae are more likely in patients with cardiac or cerebrovascular disease. Older children and elderly patients can qualify, but Jehovah's Witnesses will not accept this procedure. Autologous units are tested for HIV, hepatitis B and C, syphilis, and the human

T-cell lymphotropic virus type I. Each blood bank disposes autologous units that test positive according to their own policies. Complications can occur when autologous units are transfused, usually the result of clerical or laboratory errors or circulatory overload in the patient.

Normovolemic hemodilution is the withdrawal of a patient's whole blood and replacement with a larger volume of intravenous crystalloid—or an equal volume of colloid—which is done after inducing anesthesia and before beginning the operation. Hemodiluted patients lose fewer erythrocytes per volume of surgically shed blood. The anticoagulated withdrawn blood may be stored at room temperature for a maximum of six hours before being reinfused. Normovolemic hemodilution is contraindicated in patients in whom the compensatory increase in cardiac output is physiologically impossible or harmful.

Intraoperative blood salvage is carried out for noncontaminated, nononcologic surgical procedures that are characterized by the loss of substantial quantities of blood. Jehovah's Witnesses may be receptive to either normovolemic hemodilution or intraoperative blood salvage. The most frequently used technology for this procedure incorporates canister collection arrangements, centrifuge-based erythrocyte salvage contrivances, and supplemental washing devices. The capacity and speed of this equipment can provide almost 3 liters of saline-suspended packed cells per hour. Salvaged erythrocytes have survival times equivalent to those of homologous erythrocytes, but because intraoperative blood salvage fails to save functional platelets and clotting proteins, a dilutional coagulopathy is more likely with an increased volume of blood salvaged. Washing also removes anticoagulant used for collection and noninhalational anesthetic drugs. The potential for air embolism mandates using safeguards. Published experience now supports cautiously expanding the use of intraoperative blood salvage to selected patients having extensive cancer surgery (reducing the immunosuppressive properties of homologous transfusion); emergency traumatically contaminated body cavities (mandating a washing technique and antibiotic therapy); ectopic pregnancy; and cesarean section deliveries in which blood salvage is initiated after completing a separate and discarded suctioning of amniotic fluid from the surgical field. Unprocessed (unwashed) intraoperative blood salvage results in transfusing debris and free hemoglobin from the operative field, both of which have been implicated in cases of disseminated intravascular coagulation and organotoxicity. An absolute contraindication to the procedure is the surgical use of a microfibrillar collagen hemostat. Deliberate hypotensive anesthesia in appropriately selected patients will decrease the volume of blood obtained.

The development of clinically safe and effective oxygen carriers such as cell-free hemoglobin-based solutions and perfluorocarbon emulsions will alleviate some of the demand for blood replacement therapy.

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Alerts, Notices, and Case Reports

Simultaneous Reconstruction of the Abdominal Aorta and Cholecystectomy

A Peer Review Perspective

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THE COEXISTENCE of an abdominal aortic aneurysm and cholelithiasis is not uncommon. The surgical approach to this combined problem has been addressed by several authors.[1-8] Although opinion differs about the wisdom of attempting to resolve both problems at a single operation, there appears to be consensus that combined procedures should not be done on a routine basis. California Medical Review, Inc (CMRI), the peer review organization responsible for California's 3.2 million Medicare beneficiaries, has recently reviewed cases that demonstrate the importance of this problem to both patients and the peer review process. Claims data were reviewed to determine the frequency of aneurysmectomy in the California Medicare population, the incidence of concomitant cholecystectomy, and the hospital mortality for these procedures.

Peer review organizations were established to ensure that health care services provided and paid for by Medicare are medically necessary, of a quality that meets professionally recognized standards of health care, and supported by appropriate evidence of medical necessity and quality that the reviewing organization may be reasonably assured that the practitioner or health care provider is meeting these obligations. Medical records of the inpatient care of Medicare beneficiaries are selected and examined by nurse reviewers using generic screens to identify likely problems in the quality of care. Physician peer reviewers determine whether a possible problem exists. Should a problem be identified, a letter of inquiry is sent to the problem source (the attending physician or hospital) noting the quality concerns and requesting additional information. New information and the original medical records are forwarded for further peer review by a board-certified consultant in the specialty before a final determination is made. Based on the evidence available to the peer review organization, the issue is either resolved or determined to be a problem. In the case of a confirmed quality problem, a letter of notification is sent to the problem source specifying the nature of the problem, what should have been done, and assigning a severity level to the problem. In those cases in which the identified deficiency resulted in a significant adverse effect on the patient, a corrective action plan will be required from the responsible party to ensure that the problem is not likely to recur.

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Purpose and Design

This study was done to determine the scope of concomitant abdominal aortic aneurysm resection and cholecystectomy in the California Medicare population and, further, to determine if lessons are to be learned that may assist physicians when dealing with this clinical situation. The CMRI data base was used to determine the frequency of aneurysm resection in California Medicare recipients, the incidence of concomitant cholecystectomy, and the hospital mortality for these procedures. Hospital records of all patients who had combined procedures and either died in the hospital or were thought by peer reviewers to have had an inappropriate operation were reviewed. Cases were selected to illustrate the peer review process, surgical care that in the opinion of peer reviewers was inappropriate, and information clinicians should consider in dealing with this complex situation.

Report of Cases

Case 1

The patient, an 83-year-old man, was admitted to the hospital because of right upper quadrant abdominal pain, gallstone disease, and an aortic aneurysm. There was a history of high alcohol intake; the patient was slightly confused, and the preoperative evaluation resulted in the anticipation of an alcohol withdrawal syndrome. Gallstones had been known to be present for at least three years, and the aortic aneurysm was a recent finding. The physical examination revealed a palpable aneurysm. Sonography showed many gallstones, a dilated common bile duct, and a 5- by 6-cm aortic aneurysm. A preoperative electrocardiogram showed evidence of bradycardia and a bundle branch block. Liver function tests to include bilirubin, lactate dehydrogenase, aspartate aminotransferase, and alkaline phosphatase determinations elicited normal values.

The first operation consisted initially of clamping the aorta, opening the aneurysm, and inserting a prosthetic tube graft. The graft buckled in an unsatisfactory manner and required revision. The remaining aorta and peritoneum were used to cover the graft. The gallbladder, which was not inflamed but did contain stones, was removed. An operative cholangiogram had shown a large common bile duct but no stones. A Jackson-Pratt drain was used to drain the gallbladder bed. The abdomen was closed. Poor perfusion to the right lower extremity was immediately noted, and it was necessary to reinstitute heparin therapy, explore the right groin, and perform a right femoral embolectomy. The operating room time was longer than four hours.

After the operation the patient was initially described as confused but alert. His condition was complicated by increasing confusion thought to reflect the alcohol withdrawal syndrome, a loss of pulse in the right lower extremity on the second postoperative day, renal insufficiency, fever, hematuria, and gangrene of the right foot. The patient underwent a below-the-knee amputation and cystoscopy on the seventh postoperative day; however, his overall condition continued to deteriorate, and the patient died on the 17th day in a septic state.

Peer review. Peer reviewers were of the opinion that a combined procedure in this patient was not advisable. It was noted that a medical consultant who evaluated the patient preoperatively had indicated a "main concern" in regard to alcohol withdrawal and cardiac conduction, and an alcohol withdrawal syndrome was anticipated. The hospital record indicated that this patient had symptomatic cholelithiasis, a dilated common bile duct, and an asymptomatic aortic aneurysm. Alcoholism, age, and a cardiac conduction defect placed the patient at increased risk. The necessity of doing an operative cholangiogram and the possibility of exploring the common bile duct were thought to contraindicate a combined procedure that had the potential of exposing the aortic prosthetic graft to infection from infected bile. The vascular portion of the operation was complicated by buckling of the graft in an unsatisfactory manner that required resection of a portion of the graft and reanastomosis. At this point it was unwise to proceed with removing the gallbladder, which was not acutely inflamed. It was never clear whether the need to explore the groin and do an embolectomy had been recognized when the decision to proceed with the cholecystectomy was made.

Although the cause of death was never clearly established, two reviewers thought that intra-abdominal sepsis related to an infected graft was a major factor. The drain that was left in place for seven days may have been a source of infection. Peer reviewers commented that the most appropriate course in this patient would have been to do a cholecystectomy and defer resecting the aortic aneurysm until several weeks later.

The operating surgeon defended his practice, stating that the standard of care was to treat both conditions at the same operation and providing the article by String to support his position.[3] Unfortunately, despite the opinions of well-trained peers, the surgeon continues to believe his care was appropriate and does not recognize the need for any corrective action. Hospital and county medical society peer review committees defended the actions of the surgeon, expressing the opinion that it is an acceptable standard of practice to do an aortic aneurysmectomy and a cholecystectomy simultaneously.

Case 2

The patient, a 79-year-old asymptomatic man, was admitted for elective resection of an abdominal aortic aneurysm that had increased in size to 6 cm and a concurrent elective cholecystectomy. The patient was a long-time smoker with probable chronic pulmonary disease. An ultrasonogram showed cholelithiasis. Liver function tests including bilirubin and alkaline phosphatase measurements showed normal values. The aneurysm was palpable on physical examination.

The patient underwent resection of an abdominal aortic aneurysm, and a bifurcated graft was inserted between the aorta and iliac arteries. After the graft was inserted, bleeding was noted from the spleen. The spleen was packed in the hope that bleeding would cease, and a cholecystectomy was done. The spleen continued to bleed and was removed. Anesthesia time was more than six hours, and the patient lost eight units of blood. After the operation he continued to bleed and was returned to the operating room 12 hours later. Bleeding was found in both left and right upper quadrants at the sites of splenectomy and cholecystectomy. The patient continued to bleed and died less than 24 hours later, with death attributed to coagulopathy, the respiratory distress syndrome, and multiple organ failure.

Peer review. Peer reviewers thought the cholecystectomy was inappropriate in this patient. The patient's age and the presence of chronic pulmonary disease were thought to place the patient at increased risk. The operative note indicated that the patient had a large aneurysm with disease in both common iliacs, which made it necessary to replace the aorta with bifurcation grafts to the common femoral arteries. After all anastomoses had been completed, continued bleeding was noted, and the anesthesiologist observed the patient's blood pressure to have dropped. A tear was found in the spleen. At this point the decision was made to remove the gallbladder, which contained stones. Two units of blood were lost from the spleen while the cholecystectomy was being done. Three peer reviewers thought it was inappropriate to proceed with an elective incidental cholecystectomy in a patient who was actively bleeding and who had a fall in blood pressure. The appropriate decision would have been to remove the spleen and close the abdomen.

The surgeon responded to the peer review decision by citing the article by Ouriel and co-workers as justification for the combined procedure.[1] The hospital quality assurance committee, which included two vascular surgeons, agreed with the operating surgeon despite the fact that the cited article clearly states, "If stones are present and the aneurysmectomy has gone smoothly, cholecystectomy may be performed."[1(p719)]

Case 3

The patient, a 76-year-old man, was admitted to the hospital for elective repair of an abdominal aortic aneurysm. There was a history of abdominal pain of several weeks' duration, and an abdominal computed tomographic scan confirmed the presence of an aneurysm. The patient had sideroblastic anemia and a low leukocyte count but was otherwise thought to be in good health. Liver function tests were not done. He had a 50-pack-year smoking history.

During the operation, the patient was observed to have a thickened gallbladder containing stones. The aneurysm was opened and a bifurcation graft was inserted. The graft was covered with peritoneum and omentum. The gallbladder was removed intact. The time of the operation was slightly more than three hours. The patient did well postoperatively and was discharged home on the seventh postoperative day.

Peer review. A screening nurse questioning the necessity of the cholecystectomy referred the patient's record to a physician reviewer. The reviewer was of the opinion that in this case the risk of an incidental cholecystectomy was low and outweighed the risk of not removing the gallbladder, which contained stones. No quality-of-care issues were identified.

Discussion

The Health Services Evaluation and Research Department of CMRI provided information on three groups of patients reflecting California Medicare experience during the time period April 1, 1989, through December 31, 1991. The information was obtained from claims submitted for services to Medicare beneficiaries. Group I includes patients in whom there were resection and replacement of a nonruptured abdominal aortic aneurysm without cholecystectomy. Group II includes patients in whom resection and replacement were

done for a ruptured aneurysm without cholecystectomy, and Group III comprises patients in whom aneurysmectomy and cholecystectomy were done concomitantly. Hospital mortality in group I was 6.8% (303 of 4,468), in group II was 47.8% (469 of 981), and in group III was 6.3% (12 of 191). This appears to confirm the opinion that a concomitant cholecystectomy can be done safely in appropriately selected cases. It should not be taken as a license to remove all gallbladders containing stones in conjunction with aneurysm resection. The mortality in group III indicates that most California surgeons are selecting cases appropriately.

In 1983 Ouriel and associates reported a single instance of prosthetic infection that occurred in a patient who did not have his graft reperitonealized before cholecystectomy and no graft complications in 17 other patients who did have their grafts reperitonealized before cholecystectomy.[1] Concomitant aneurysmectomy and cholecystectomy were advised in those patients with cholelithiasis undergoing aortic aneurysm resection, providing no contraindications exist. String advised cholecystectomy for patients undergoing aortic reconstruction who had associated cholelithiasis if there were no mitigating circumstances.[3] Should common bile duct stones or ductal enlargement be identified, String advised it would be more expedient to return another day, rather than expose the intraductal system. Vanek recommends cholecystectomy as a concomitant procedure if no complications exist and the patient's condition is stable.[6] He also thought that, if a patient was undergoing laparotomy for another reason and an aortic aneurysm was found to be present, the aneurysm should be resected only if it is large, symptomatic, or ruptured. In the opinion of Calligaro and Veith, the finding of gallstones at an operation should prompt the surgeon to do a cholecystectomy if it is technically easy.[7] Sonpal and colleagues conclude that as long as the gallbladder is easily accessible and the condition of the patient warrants the additional time, an incidental cholecystectomy should be done.[8]

Enthusiasm for performing cholecystectomy after placing a prosthetic graft is not shared by all authors. In reviewing the Mayo Clinic (Rochester, Minnesota) practice, Bickerstaff and co-workers found an unsuspected increase in morbidity in patients who underwent cholecystectomy as a secondary procedure and suggested prudence and caution in contemplating aneurysm repair and a concomitant procedure.[2] In Fry and Fry's view, cholecystectomy and aortic reconstructions rarely need to be done concomitantly and then only in those patients in whom the risk of not treating both biliary and aortic conditions is greater than the operative risks.[4] Buckles and Wilson think the practice of concurrent nonvascular procedures during vascular reconstruction cannot be recommended.[5]

Of interest is that in both case 1 and case 2, the surgeons insist they have provided appropriate care to their patients. They accepted neither the findings nor opinions of their peers, and there has been no participation in a corrective action plan. Although CMRI has the option of recommending a sanction, it is unlikely to be done based on a single case. The organization would much prefer an educational intervention, but unfortunately some physicians are not receptive to constructive criticism from their peers. Peer review organizations would prefer to be looked on as educational rather than punitive organizations, but in many cases educational interventions are of questionable value,[9] and other interventions may have to be considered.

In these cases it cannot be concluded that the concomitant cholecystectomy was responsible for the patients' deaths, nor do we think that all concomitant procedures are to be found inappropriate or unnecessary, as evidenced by approval in case 3. CMRI does require each case to be decided by peer review and, further, that physicians can provide better care after listening to their peers and accepting constructive criticism. Concomitant aneurysmectomy and cholecystectomy may be appropriate in certain cases. Routinely applying combined surgical procedures in all patients would not be beneficial to Medicare patients and, indeed, patients in general.

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Diffuse Demyelinating Lesions of the Brain After the Rapid Development of Hypernatremia

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Presented as a poster at the Indiana regional meeting of the American College of Physicians, Indianapolis, Indiana, November 28, 1990.

CENTRAL PONTINE MYELINOLYSIS, first described in 1959,[1] is characterized by dysarthria, dysphagia, mutism, and quadriparesis. Previous reports have proposed several causes, with severe hyponatremia and its correction having received the most attention.[2,3] The link between the rapid correction of severe hyponatremia to mild hyponatremia and central pontine myelinolysis has been questioned, however.[4] Hypernatremia has also been implicated in this disorder.[5-7]

Extrapontine myelinolysis often accompanies pontine lesions in the same clinical circumstances. The lesions produced by both of these disorders, detected either by autopsy or radiographic techniques, have been called "cerebral demyelinating lesions" by Ayus and co-workers.[5] I report a case of combined pontine and extrapontine myelinolysis that

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TABLE 1.—*Daily Serum Sodium Cancentratian and Effective Plasma Osmolality in a Patient With Hepatic Encephalopathy*

Laboratory Value	Hospital Day 1	2	3	4	5	6	7	8
Serum sodium, mmol/liter	142	148	166	161	147	140	143	141
Serum glucose, mmol/liter	10.3	9.1	23.0	8.5	17.5	23.6	5.6	4.4
Plasma osmolality, mOsm/kg*	294	305	355	331	312	304	292	286

*The effective plasma osmolality was calculated using the following equation: Osmol = 2(Na^+) + Glucose where Glucose = the serum glucose concentration.

occurred after the rapid development of hypernatremia. Presenting with hepatic encephalopathy, the patient initially had a normal serum sodium concentration.

Report of a Case

The patient, a 57-year-old woman, was admitted because of lethargy for two days. She had numerous previous admissions for hepatic encephalopathy and upper gastrointestinal tract bleeding. Ethanol abuse was the cause of her chronic liver disease. Several upper endoscopic procedures in the past had shown esophageal varices. The construction of a superior mesenteric vein-inferior vena caval shunt six years before admission failed to prevent recurrent bleeding episodes. Her other medical problems included diabetes mellitus and hypertension.

At admission she was lethargic but able to be aroused. The only abnormal finding on physical examination was guaiac-positive stool. Her neurologic state on examination was physiologic, and there was no asterixis. Serum electrolyte values were as follows: sodium, 142 mmol per liter; potassium, 2.9 mmol per liter; chloride, 113 mmol per liter; and bicarbonate, 27 mmol per liter. Other serum laboratory values included glucose, 10.3 mmol per liter (normal, 3.9 to 6.1); albumin, 33 grams per liter (normal, 35 to 50); and arterial ammonia, 79 μmol per liter (normal, 7 to 21). A lumbar puncture yielded grossly bloody cerebrospinal fluid thought secondary to trauma. The corrected leukocyte count was 0 cells per μl, the glucose concentration was 6.0 mmol per liter (normal, 2.2 to 3.9), and the protein level was 2.58 grams per liter (normal, 0.15 to 0.45). Computed tomography of the head showed severe atrophy and a questionable lacunar infarction of the left thalamus.

The admission diagnosis was hepatic encephalopathy, and lactulose enema therapy was begun. Hyperglycemia was treated with frequent doses of short-acting insulin. By hospital day 3, about 36 hours after admission, the serum sodium concentration had risen to 166 mmol per liter, and the glucose concentration was 23.0 mmol per liter. There was evidence of volume depletion on examination, and a hyperchloremic metabolic acidosis (arterial pH 7.29) had developed. The frequency of lactulose administration was decreased. The following day, the serum sodium concentra-

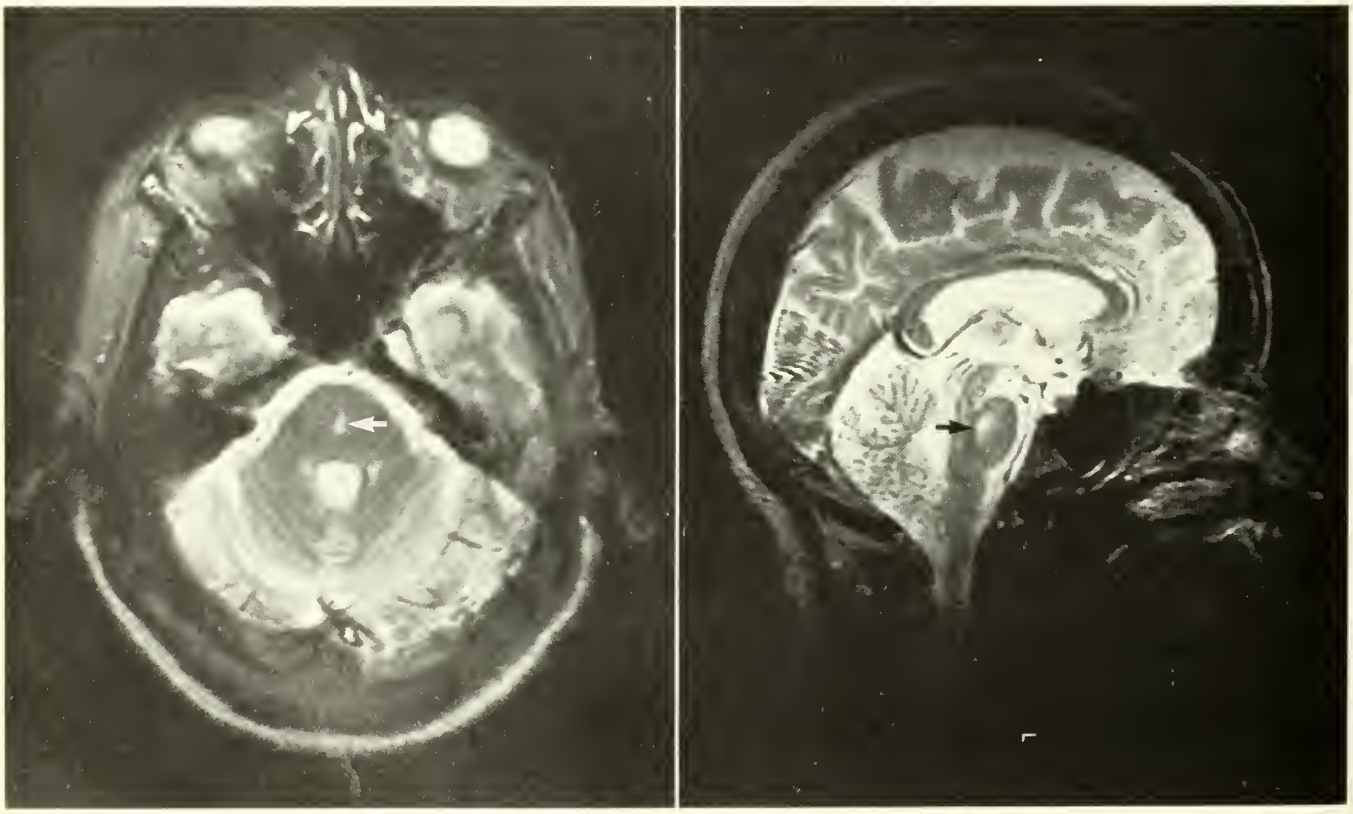

Figure 1.—A T2-weighted intracranial magnetic resonance imaging study is shown. A focal area of abnormally increased signal in the central pons **(arrow)** is seen on both the axial **(left)** and sagittal **(right)** views.

tion fell to 161 mmol per liter, the arterial ammonia concentration decreased to 41 μmol per liter, and the metabolic acidosis was resolving. In addition, the patient was able to follow simple commands for the first time. The hypernatremia had completely resolved by hospital day 6, at which time she was alert and fully oriented. Her speech was normal. Daily serum sodium concentrations and effective plasma osmolalities are shown in Table 1.

Clinical improvement continued until hospital day 10, when dysarthria, difficulty with swallowing, and drooling became evident. Mutism subsequently developed. A neurologic evaluation revealed pronounced weakness of the tongue, palate, and muscles of mastication in addition to quadriparesis and bilateral Babinski's signs. The muscle stretch reflexes were symmetrically brisk. Intracranial magnetic resonance imaging showed an abnormally increased signal in the central pons (Figure 1). There were also multiple focal areas of abnormally increased signal in the periventricular white matter.

The clinical diagnosis of central pontine myelinolysis with extrapontine myelinolysis was made. The patient underwent intensive physical therapy and gastric tube placement. Six weeks later, she was able to feed herself. Her speech has improved but is still slurred. She can ambulate with assistance.

Discussion

The association of severe symptomatic hyponatremia with central pontine and extrapontine myelinolysis has been a widely studied and debated topic.[4,5] Although less commonly reported, the association of hypernatremia with cerebral demyelinating lesions in at least three clinical settings has been recognized. Ayus and colleagues found the following clinical situations to be associated with myelinolysis[5]: the overcorrection of hyponatremia, the development of hypernatremia in patients with hepatic encephalopathy, and an increase in the serum sodium concentration of more than 25 mmol per liter in the first 48 hours of hospital admission. The second situation clearly applies in this case. In addition, the patient's increase in serum sodium concentration of 24 mmol per liter in the first 48 hours approximates the value in the third criterion.

The patient presented with a normal serum sodium concentration, and the administration of lactulose most probably caused the severe hypernatremia. The osmotic diarrhea created by lactulose therapy has been shown to cause hypernatremia.[8,9] In addition to hypernatremia, hyperglycemia contributed to her osmotic insult. Similar cases of pontine with extrapontine myelinolysis associated with severe hyperosmolality due to combined hypernatremia and hyperglycemia have been described.[7,10]

Several reports have emphasized the association of both alcoholism and chronic liver disease with these lesions.[1,3,7] Although the patient had begun abstaining about two years before admission, she had alcoholic liver disease. Cases of combined central pontine and extrapontine myelinolysis have also been described in patients who have had liver transplants. Large perioperative increases in the serum sodium concentration have been implicated in this group.[11]

In this patient, hypernatremia was a risk factor in the development of myelinolysis. One group of investigators recently postulated that any rapid and large increase in the serum sodium concentration may lead to cerebral demyelinating lesions in a patient with preexisting liver disease.[11] This case corroborates that speculation. The presence of hepatic encephalopathy may enhance the chance of this occurring.

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Adult Still's Disease Presenting as Fever of Undetermined Origin in a Patient With Leukemoid Reaction

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FEVER OF UNDETERMINED ORIGIN (FUO) poses one of the most difficult diagnostic challenges to clinicians. Arriving at the correct diagnosis requires repeated assessment of the physical examination, laboratory, and radiologic data. The leukocyte count if elevated generally indicates infection. Some patients with the most extreme leukocytosis (leukemoid reaction), however, may have a disease that is noninfectious. We describe the case of a patient with adult Still's disease that presented as an FUO with leukemoid reaction. A discussion of the differential diagnosis of leukemoid reaction in FUO follows.

Report of a Case

The patient, a 23-year-old man, was admitted because for two weeks he had had pleuritic chest pain, myalgias, fever with chills, and nonproductive cough. He gave a history of recent heavy alcohol intake. He had been admitted to another hospital a week before with similar symptoms. A chest x-ray film at that time showed small bilateral pleural effusions and

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a patchy right lower lobe infiltrate. He signed out against medical advice after receiving antibiotic therapy for several days without a clinical response. On admission to Cook County Hospital (Chicago, Illinois), the patient was found to have tachypnea with respirations of 36 per minute, a pulse rate of 108 beats per minute, and a temperature of 39.6°C (103.3°F). The chest was clear to auscultation, heart sounds were normal, and the abdominal examination revealed tender hepatomegaly with normal bowel sounds. His sclerae were nonicteric. No skin rashes were noted. A chest x-ray film showed patchy infiltrates in the right lung base and small bilateral pleural effusions.

Initial laboratory studies elicited the following values: leukocyte count, 54.5×10^9 per liter (0.96 neutrophils); hemoglobin, 140 grams per liter; platelet count, 503×10^9 per liter; aspartate aminotransferase, 76 U per liter; alanine aminotransferase, 67 U per liter; cholesterol, 2.69 mmol per liter (104 mg per dl); total bilirubin, 24 μmol per liter (1.4 mg per dl); alkaline phosphatase, 179 U per liter; γ-glutamyl transferase, 262 U per liter; total protein, 60 grams per liter (6.0 grams per dl); albumin, 26 grams per liter (2.6 grams per dl); prothrombin time, 14.5 seconds; partial thromboplastin time, 37.6 seconds; and erythrocyte sedimentation rate, 61 mm per hour. Arterial blood gas determinations while the patient was breathing room air revealed pH 7.49, P_{O_2} 64 mm of mercury, P_{CO_2} 30.5 mm of mercury, and bicarbonate 23 mEq per liter.

Alcoholic hepatitis was considered as a possible diagnosis based on the recent history of heavy alcohol intake, tender hepatomegaly, and the high leukocyte count. Abdominal ultrasonography showed hepatomegaly with decreased echogenicity on several images, suggesting hepatitis. No ascites was noted. A liver biopsy was done, and the specimen showed focal sinusoidal dilation with increased sinusoidal collagen deposition (nonspecific findings). Atypical pneumonia was also considered, and treatment with erythromycin was started. Attempts to tap the pleural effusion under ultrasonography were unsuccessful. *Mycoplasma* titers and cold agglutinin levels were not elevated. The patient continued to have a remittent fever profile with spikes as high as 40°C (104°F). Erythromycin therapy was discontinued and an empiric course of doxycycline was begun. A hepatitis screen was negative for hepatitis B surface antigen and antibody.

The serum bilirubin level rose to a maximum of 62 μmol per liter (3.6 mg per dl). A macular skin rash then developed over the patient's trunk and extremities. This coincided with an increase in myalgias and the development of arthralgias with effusions in both knees. A serum antinuclear antibody test was negative, and complement levels were normal. The leukocyte count remained elevated in the range of 35 to 45×10^9 per liter. The leukocyte alkaline phosphatase level was markedly increased to 353 U per liter. An arthrocentesis of the left knee joint showed 1.7 leukocytes $\times 10^9$ per liter (0.60 neutrophils) with a protein content of 29 grams per liter (2.9 grams per dl). The patient continued to have temperature spikes to 39.4°C (103°F) on doxycycline therapy, which was subsequently discontinued after about a week.

A diagnosis of adult Still's disease was considered, and the patient was started on a course of prednisone, 30 mg a day, which was eventually increased to 60 mg a day with the addition of aspirin. On this regimen, he defervesced and his joint symptoms resolved. Records obtained at the time of discharge revealed a previous hospital admission at age 7 years for an undefined febrile illness characterized by leukocytosis (as high as 47×10^9 per liter), anemia, an elevated sedimentation rate, pericarditis, and a clinical response to steroid therapy.

Discussion

Krumbhaar introduced the term "leukemoid reaction" in 1926 to describe leukocytic features that could mimic leukemia and that included both leukocytosis and leukopenia.[1] Leukemoid reactions associated with various leukocyte types—neutrophils, lymphocytes, monocytes, eosinophils, and basophils—have been described.[2] Myeloid leukemoid reactions with leukocyte counts in excess of 40 to 50×10^9 per liter may occur in several disorders[2,3]:

- Malignant neoplasms, especially if associated with superimposed infections, may manifest as pronounced leukocytosis, commonly with mature neutrophils. Counts as high as 120×10^9 per liter have been reported;
- Malignant disease with bony metastases may be associated with a notable shift to the left with myeloblasts, promyelocytes, and myelocytes, as seen with chronic myelocytic leukemia;
- Leukemoid reactions simulating acute myeloblastic or promyelocytic leukemia may be seen during infection in several groups of patients: those with compromised marrow reserves such as in alcoholism, in patients with vitamin B_{12} or folate deficiency, or in those previously treated with myelosuppressive drugs;
- Miliary tuberculosis has been reported to occur in association with either a high neutrophil count or a pronounced left shift.

Leukemoid reactions in patients with malignant neoplasms most commonly occur in carcinoma of the lung, followed by cancers of the kidneys, thyroid, stomach, liver, pancreas, and urinary bladder.[4] It is unusual for malignant disease to present with a leukemoid reaction because it tends to occur late in the course.[4] Carcinoma of the kidneys or pancreas, however, is more likely to remain undiagnosed until a relatively late stage and could present with a leukemoid reaction. Carcinoma of the kidneys or pancreas may also be associated with fever.[5] Lymphomas and Hodgkin's disease, which are common causes of FUO, are rare causes of leukemoid reaction.[4]

As mentioned, miliary tuberculosis has been described as presenting as FUO with prominent leukocytosis, particularly in elderly patients.[6] Occasionally tuberculosis may manifest hematologically with immature forms or with pancytopenia.[6] Controversy exists as to whether leukemia observed in these patients is due to tuberculosis or whether it represents true leukemia.[7]

Malaria is a rare cause of leukemoid reaction that could present as FUO.[5,8] Shigellosis is a well-known infectious cause of leukemoid reaction but generally causes symptoms referrable to the gastrointestinal tract.[9]

Alcoholic hepatitis is a noninfectious cause of leukemoid reaction and FUO that can produce high spiking fever, minimal jaundice, and normal or only minimally elevated liver enzyme levels.[10] Leukocyte counts in the range of 100×10^9 per liter have been described. A high leukocyte count in a patient with alcoholic hepatitis is considered a poor prognostic sign.[11] Prominent leukocytosis and fever can be seen in patients with vasculitis, notably polyarteritis nodosa.[12] Fa-

milial Mediterranean fever can occur as fever and leukocytosis in the range of 30 to 40 × 10^9 per liter.[13]

Adult Still's disease has been described as presenting in adults as FUO,[14] with a symptom complex variably consisting of high fever, arthralgias or arthritis, an evanescent skin rash, lymphadenopathy, splenomegaly, myocarditis, pericarditis, and pneumonitis.[14] The average age at presentation is in the mid-20s. Hepatic abnormalities generally consist of mild hepatomegaly and modest elevations of aminotransferase levels, although more severe hepatic involvement has been described.[15] Prominent leukocytosis with leukocyte counts in excess of 18 × 10^9 per liter is commonly seen. About 20% of patients have self-limited systemic disease.[15] Treatment consists of administering salicylates, nonsteroidal anti-inflammatory drugs, and corticosteroids.

In our patient, alcoholic hepatitis and vasculitis were major alternative diagnostic considerations. Alcoholic hepatitis was dismissed largely on the absence of characteristic pathologic findings on liver biopsy as well as the findings of skin rash, lung involvement, and arthritis that could not be explained on the basis of alcoholic liver disease. Several syndromes of vasculitis have been described in association with FUO[12]: classic polyarteritis nodosa, giant cell arteritis, Wegener's granulomatosis, and hypersensitivity vasculitis. Regarding polyarteritis nodosa, the patient would be young for this disease, and there was no evidence of renal involvement or hypertension. In addition, liver involvement in polyarteritis nodosa has been described, to our knowledge, only in patients who have positive serologic tests for hepatitis B (negative in this patient). Also, lung involvement is unusual in polyarteritis nodosa, the liver biopsy showed no evidence of arteritis, and the skin rash was atypical for vasculitis. In consideration of giant cell arteritis, the patient was young for this disease as well, and headache and visual disturbances were absent. Hepatic involvement is unusual in giant cell arteritis. A lack of nasal or renal involvement would make Wegener's granulomatosis unlikely. Finally, in hypersensitivity angiitis, the characteristic clinical features are cutaneous lesions.[12] The evanescent rash manifested by our patient would be distinctly unusual for hypersensitivity angiitis where hemorrhagic purpura (leukocytoclastic vasculitis) is generally seen.

In summary, the differential diagnosis of FUO with leukemoid reaction includes both infectious and noninfectious causes. As illustrated by this case, adult Still's disease should be a diagnostic consideration.[14,15]

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Special Series

Costs and Coverage
Pressures Toward Health Care Reform

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Signs of discontent with the health care system are growing. Calls for health care reform are largely motivated by the continued increase in health care costs and the large number of people without adequate health insurance. For the past 20 years, health care spending has risen at rates higher than the gross national product. As many as 35 million people are without health insurance. As proposals for health care reform are developed, it is useful to understand the roots of the cost problem. Causes of spiraling health care costs include "market failure" in the health care market, expansion in technology, excessive administrative costs, unnecessary care and defensive medicine, increased patient complexity, excess capacity within the health care system, and low productivity. Attempts to control costs, by the federal government for the Medicare program and then by the private sector, have to date been mostly unsuccessful. New proposals for health care reform are proliferating, and important changes in the health care system are likely.

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This paper is the first in a series on health care reform.

Early this year, as signs of discontent continued to build about the United States health care system, an experienced observer of the health policy process was led to remark, "There will be no more politics as usual" (E. B. Dowell, former Director of Governmental Affairs, Blue Cross of California, oral communication, April 1992). After years of neglecting issues related to health care, except for a limited interest in the acquired immunodeficiency syndrome (AIDS) epidemic, the media have suddenly turned their attention to this subject. In addition to national newspapers, in the past year *Time*, *Fortune*, *The National Journal*, and *Business Week* have run cover stories on the health care crisis. Public television produced a special program on health care, and major news programs, "60 Minutes" and the "MacNeil/Lehrer NewsHour," dedicated segments to this dilemma. Media activity increased rapidly throughout 1991, and issues concerning management of the health care system have shown the greatest increase in media activity (*IssueScan*, 4th quarter, 1991).

A survey conducted by Louis Harris and Associates in 1988 found that 89% of Americans wanted to see a dramatic change in the health care system: 29% thought that the health care system needs to be completely rebuilt, and an additional 60% thought that the system needs fundamental changes.[1] A poll conducted by *Time* and the Cable News Network found that 91% of Americans thought that the health care system needs fundamental change, and 75% of those surveyed said that costs are much higher than they should be (J. Castro, "Condition: Critical," *Time*, November 25, 1991, p 34). A poll in 1990 found only 10% of Americans satisfied with the current health care system, in contrast to 56% in Canada, 41% in West Germany, and 22% in Great Britain.[1]

The results of many of these polls were summarized in 1991 by Blendon and Donehue:

> Opinion polls indicate that support for a national health plan is at a 40-year high point and more than 10 national and statewide surveys conducted since 1989 indicate that between 60 and 72 percent of Americans are in favor of such a plan . . . . By some of these measures, the public's enthusiasm for the concept of a comprehensive program of national health insurance exceeds the level of support for Medicare in the year prior to its enactment. In fact, a recent Roper Organization survey indicates that 69 percent of all Americans surveyed would approve extending Medicare coverage to all citizens.[2(pp173-175)]

More recent polls indicate continuing discontent with the present system, particularly the high costs of care. In an exit poll after the Pennsylvania special senatorial election in November 1991, people were asked what they thought was the biggest problem with health care for themselves and their families; 77% of the voters responded that the biggest problem was cost. Voters in the New Hampshire primary cited health care and national health insurance as the second most important factor in deciding their votes—after the recession and concerns for the economy ("Health Reform Number Two Issue in New Hampshire," News Release, Henry J. Kaiser Family Foundation, Menlo Park, Calif, February 1992). The most recent Kaiser/Commonwealth Health Insurance Survey found that Americans are increasingly dissatisfied with their health care and with the health care system ("Survey Shows Widespread Public Concern About Health Insurance Coverage and Costs," News Release, Henry J. Kaiser Family Foundation, Menlo Park, Calif, April 1992) and that 60% of Americans think it is the responsibility of government to provide health insurance to all, compared with 34% who believe it is the responsibility of the private sector.

Clearly the public perceives a problem that stems from the high cost of health care, and they call for the federal government to engineer major reforms. Research by the Public Agenda Foundation, in association with the Gallup organization and the Employee Benefit Research Institute,[3]

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
GNP = gross national product
HCFA = Health Care Financing Administration

suggests that the public is particularly concerned about out-of-pocket costs. According to the Public Agenda Foundation, people attribute high costs to "unnecessary tests, overpaid doctors, wasteful hospitals, profiteering drug companies, and greedy malpractice lawyers."[3(p4)] Surveys have found that the great majority of the public thinks that spending on physician services is too high and that physicians are too interested in financial reward.[4]

The general public concern is that physician fees are too high, and, in fact, physicians' real earnings have increased considerably in the past decade. Average inflation-adjusted physician income grew by 24% from 1982 to 1989.[5] This increase was not spread equally across all specialties, however, with some experiencing only modest gains as others reaped dramatic increases. In areas like family practice and internal medicine, income levels have been relatively flat.

Although Medicare policy changes to control costs have been enacted by Congress since 1983, little interest has been shown for systemic reforms until recently. Only in the past year has the notion of a major federal role in cost containment for the private sector begun to attract serious attention. In recent years, more than 40 bills have been introduced in Congress, ranging from incremental changes in health insurance and malpractice reform to sweeping "top-down" reform. The three basic approaches before Congress are a market approach, a single-payer approach, and a "play or pay" approach.[6,7]

At the state level, discontent is also evident, particularly with reduced state revenues and climbing Medicaid expenditures.[8] Minnesota recently enacted a plan to cover the uninsured,[9] and more than 30 states are considering major health care reforms.

Physicians agree that there is a problem, although they tend to focus on the uninsured rather than on rising costs. Health care reform issues are beginning to attract attention within medicine. The American Medical Association, the American College of Physicians, and the American Academy of Family Practice all supported the Medicare fee schedule included as part of the 1989 Medicare physician payment reforms enacted by Congress. One of the first physician-authored health care reform proposals, set forth by the Physicians for a National Health Program, appeared in an article published in January 1989.[10] The landmark May 15, 1991, issue of the *Journal of the American Medical Association* and now a second special issue dedicated to health care reform proposals illustrate a broad, open approach, in contrast to the past when most proposals suggesting government intervention were rejected out of hand by physician organizations. Indeed, the American Medical Association has endorsed the idea of government-mandated private insurance coverage[11] and has hinted that it might support some form of overall cost containment. The California Medical Association qualified a proposition for the November 1992 ballot called Affordable Basic Care that would require employers to provide health insurance for their employees.[12] In September 1992 the American College of Physicians published their plan for systemwide reform in the organization and financing of health care.[13]

Factors Driving Reform—Rising Costs and the Uninsured

Growing calls for health care reform in the United States are largely the result of two factors: the continued increase in health care costs, which have been well above increases in gross national product (GNP) for most of the past 20 years, and the large number of uninsured and underinsured.[14] In addition, as costs increase, employer coverage is deteriorating. Millions of people will not change jobs for fear of losing their employment-based private health insurance. This is due in part to the erosion of risk-pooling and the increasing use of experience rating, the practice of pegging a group's insurance premiums to its historical use patterns. This practice is in contrast to community rating, which charges insurance premiums based on the experience of an entire community rather than a small group. Insecurity about changing health plans is further exacerbated by preexisting condition clauses that exclude or impose restrictions on coverage for health problems documented at the time of enrollment. Finally, it is a matter of increasing concern that the United States does not compare well with other industrial democracies in universal coverage, cost containment, and health status.

Rising Health Care Costs

The most important factor propelling health care reform in the United States is the cost of health care, both in absolute terms and in the rate of cost increases. A few figures tell the story. Measured in current dollars, health care spending in the United States between 1970 and 1990 rose at an annual rate of 11.6% whereas national income, as measured by the GNP, increased at an average annual rate of 8.8%.[5] As a result, the share of the GNP devoted to health care grew by more than half in 20 years: from 7.3% to 12.3%. The Commerce Department predicts that the share of the GNP devoted to health care will rise to 14% in 1992. The Health Care Financing Administration (HCFA) projects that health care will absorb more than 16% of the GNP by the year 2000.

The pluralistic nature of health care financing means that persons, families, insurers, employers, and government at all levels (federal, state, and local) are affected by high costs. Steuerle estimated that total US health care expenditures in fiscal year 1992 will be $768 billion, drawn from the following sources of financing: individuals (out of pocket), private health insurance (employer's share), Medicare, Medicaid, other public programs, federal tax subsidies, private health insurance (employee's share), other private sources, and state tax subsidies (Figure 1).[16]

In the end, it is families and individuals who bear the financial burden. In his report, Steuerle analyzes the cost to families in a manner that reveals the true cost of health care.[16] He estimates that the average expenditure per household is $8,000 per year. Of this, only about a third is paid directly by household members. The largest costs are indirect, particularly through taxes that finance public programs and reduced wages that are siphoned into insurance premiums paid by employers (Table 1).[16]

Spiraling costs are also endured by Medicare beneficiaries. Although Medicare is a major source of financial security for older Americans, the proportion of their income spent on health care is increasing. In 1972 they spent 10.6%

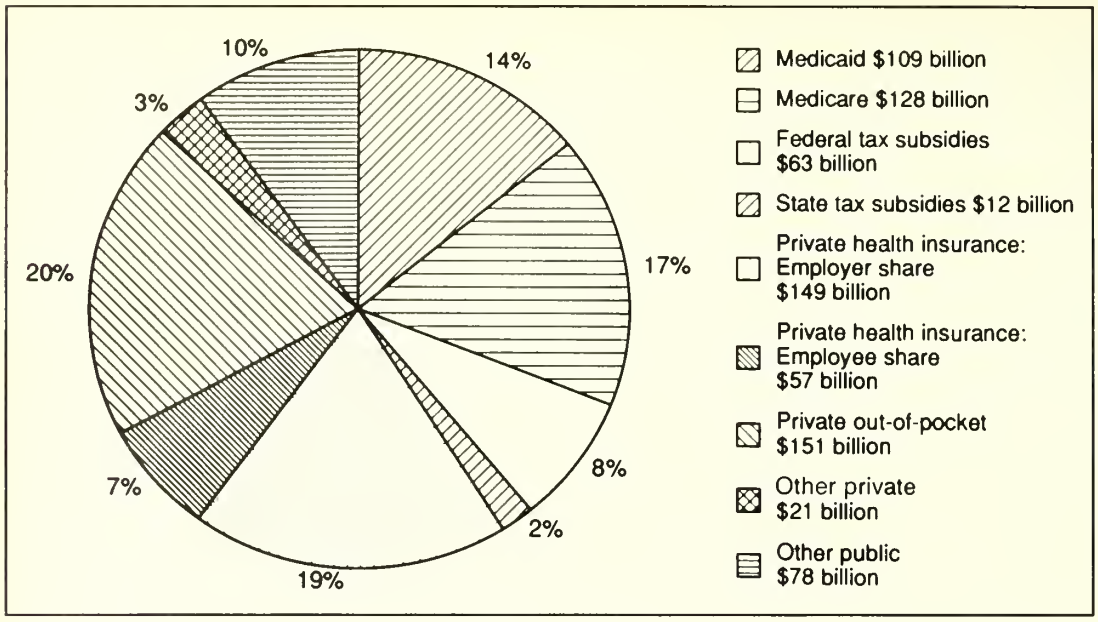

Figure 1.—The graph shows the estimated sources of financing for United States health care expenditures, fiscal year 1992 (adapted from Steuerle[16]).

of their income on health care. This rose to 16.2% in 1984 and 17.1% in 1991.[17] The bulk of the increase has been in Medi-Gap premiums and direct out-of-pocket costs—deductibles and coinsurance for private health insurance and Medicare Part A and Part B; balance bills and uncovered services, such as prescription drugs; and nursing home costs.

Health care is also taking a growing portion of federal funds. In 1970, spending on health constituted 7.1% of the federal budget, a share that rose to 13.4% in 1990. The Congressional Budget Office projects that health care will account for more than 20% of the federal budget by 1996.[18] Although federal health expenditures are projected to rise by 7.0% annually, Social Security expenditures are expected to rise by 2.2%, net interest on the debt 1.4%, and the percentages devoted to all other federal expenditures are expected to decline.[19]

Uninsured Americans

The second major factor stimulating a host of health care reform proposals is the growing population of uninsured persons. Most estimates place the number of Americans without public or private health insurance between 31 and 36 million.[20] The 1987 National Medical Care Expenditure Survey found that 18.5% of the population (47.8 million Americans) lacked health insurance for all or part of 1987. On any given day, between 34 and 36 million were uninsured, and 24.5 million were uninsured throughout the year.[14] Analysis of the March 1990 Current Population Survey found that 33.4 million people (13.6% of the population) had no health insurance (public or private) throughout 1989.[21] Thus, millions of people in this country lack access to even the most basic health services.

The 1987 survey found that of the uninsured population, 70% were employed or dependents of employed persons. Approximately 10% are unemployed persons and their dependents, and the remainder are nonworkers, such as students.[14]

The number of uninsured increased rapidly between 1979 and 1984, from 28.8 million in 1979 to 37.3 million in 1984.[14] The most notable factor in the rising number of unin-

TABLE 1.—*How US Households Pay for Health Care**

Estimated Costs, 1992	*Average per Household, $*	*Percent of GNP*	*Percent of Personal Income*
Paid indirectly			
Taxes			
Federal hospital insurance payroll tax	860	1.4	1.6
Other federal, state, and local†	3,070	4.9	5.8
Reduced wages (paid by employers)‡	1,580	2.5	3.0
Other§	190	0.3	0.4
Paid directly			
Personal contributions to private health insurance‖	590	0.9	1.1
Out-of-pocket payments	1,580	2.5	3.0
Premiums			
Federal supplemental medical insurance	130	0.2	0.2
Total	8,000	12.9	15.1

GNP = gross national product

*Adapted from Steuerle.[16]

†Includes taxes needed to finance direct government health spending out of general revenues, plus the amount of general taxes that must be raised to compensate for revenue lost due to special tax treatment of certain health-related income (about 26% of total).

‡Employer contributions for health insurance, less government tax subsidies.

§Nonpatient revenue for the health care industry, such as charitable donations, interest income, hospital parking, and gift shops.

‖Includes employee contributions to private group health insurance plans and individual policy premiums.

sured Americans was the recession of the early 1980s. From 1984 through 1989 the number of uninsured seems to have stabilized. It is not yet clear what effect the current recession has had on the number of uninsured persons. Unemployment is currently more than 7% nationwide (B. Holey, Bureau of Labor Statistics, US Department of Labor, oral communication, September 1992), and it is even higher in some regions, such as California, where it is 9.5%. Signs of an economic recovery are still faint.

The continuing realignment of the economy, with changes in the mix of industries and occupations, is also contributing to the rise in the number of uninsured. The volume of jobs in the manufacturing sector is declining as the service sector is growing. The manufacturing sector has a strong union tradition with generous employee benefits. Whereas 90% of persons working in manufacturing had health insurance in 1990,[21] employees in most other sectors of the economy did not receive health benefits at this level. Of those employed in agriculture 30% did not have health insurance, and of those in service sector jobs 25% did not.[21] Also, the erosion of Medicaid in many states has resulted in a growing number of poor without Medicaid eligibility. Where 65% of the poor were once eligible for Medicaid, the program now covers less than 40% of the population below poverty.[22]

Lack of public or private insurance coverage ranges from less than 10% in 13 states, including Hawaii, Massachusetts, Connecticut, Michigan, Wisconsin, and Iowa, to more than 20% in Texas, Louisiana, and New Mexico.[21] California has the largest number of uninsured, a figure that has climbed to 6 million.[23] Uninsured persons are found in disproportionate numbers among those 18 to 28 years of age, Hispanics and African Americans, those with low incomes, and those living in rural areas.[14]

A lack of insurance has several important consequences. It places a substantial financial burden on persons and families with relatively low incomes. High costs reduce access to care for appropriate services. Poor access to primary care is associated with increased health care costs and decreased health status.[24]

Factors Contributing to Rising Health Care Costs

As problems related to costs and the uninsured motivate policymakers to explore ways to improve or revamp the medical care system, assessments of various proposals must consider how they address these twin issues. As will be seen in subsequent articles in this series, most of the current crop of proposals offer some detail on how they will address the problem of insurance coverage. Specifics on how costs will be contained are less often available. To assess the plausibility of various approaches, it is helpful to examine first the causes of spiraling health care costs.

The rise in personal health care expenditures can be broken into four components: general inflation, as measured by the consumer price index; population growth; medical care price inflation above general inflation; and all other factors, including increases in volume and intensity of services. Whereas the components that are not controllable within the health care system—general inflation and population growth—accounted for about 55% of the increase in the past 20 years, medical care price inflation has accounted for 17% of the increase and the volume and intensity of services for approximately 28%.[25]

It is difficult to differentiate the effects of medical care inflation, quality improvements, and increased volume and intensity. This collection of components, however, is affected by a variety of factors, including,

- Market failure,
- Technology,
- Administrative costs,
- Unnecessary care and defensive medicine,
- Patient complexity,
- Excess capacity, and
- Productivity.[26]

Market Failure

Market failure is an economic term describing a situation in which normal marketplace behavior cannot be assumed to lead automatically to an efficient allocation of resources. In this context "failure" is a technical explanation of the common observation that medical care is different from other goods and services. Five factors contribute to market failure in the United States: Suppliers may influence demand, consumers are usually cost "unconscious" when using medical care, workers are shielded from the true costs of insurance, uncertainty in the services needed for treating individual patients leads to the predominance of fee-for-service reimbursement, and information is lacking on what works.

An inherent aspect of medical care, regardless of the organizational and economic system, is uncertainty at the outset concerning the need for and efficacy of specific treatments. Arrow's classic article on this issue laid the groundwork for the field of health economics.[27]

In the United States, the consumers' desire to insure against the risk of costly medical care led to the growth of private health insurance, both employment-based and self-purchased. The number of companies providing group health insurance has grown from only 37 such companies in 1942 to more than 1,500 companies today. Although about 100 companies provide coverage to 90% of the covered population, and an additional 250 companies provide most of the rest, hundreds of other companies provide some type of health coverage (H. Raymond, Health Insurance Association of America, oral communication, May 1992).

Fragmentation of the insurance market has several deleterious effects. First, because providers are reimbursed by many insurers, each company represents a small fraction of a physician's caseload. Thus, it is impossible for an individual carrier to collect valid information about a provider's quality and practice style. It also becomes infeasible to negotiate average payment rates for episodes of care as an alternative to fee-for-service reimbursement while protecting physicians from costs associated with treating patients with unusually complicated conditions. Second, competition among insurers for enrollees leads to fragmentation of the risk pool (those being insured) because of the voluntary nature of health insurance and the fact that more and more insurers use experience rating. Voluntary enrollment means that a given premium will be most attractive to those most in need of treatment. Because of this, insurers will seek to avoid high-risk enrollees.

Technology

Developments in technology—new drugs, devices, and procedures—play an important role in improving the quality and effectiveness of health care and in escalating costs. After pharmaceuticals are developed and approved as safe and ef-

fective for specific indications, their application may be broadened, and they may be used when they are only marginally effective or even ineffective. Diagnostic technologies such as endoscopy, computed tomographic scan, and magnetic resonance imaging may also be used initially for a limited number of indications, but gradually the application is broadened, and there may be misuse, overuse, and underuse.

During the past 30 years, faculty at the Institute for Health Policy Studies at the University of California, San Francisco,[28-30] and the Palo Alto (California) Medical Foundation,[31,32] as well as other investigators[33] have studied the effects of medical technology on costs. Studies in the 1960s strongly suggested that for most conditions it was "little ticket" items that contributed most to expenditure increases, and technology was not driving up costs. By the mid-1970s this began to shift, and studies in the 1980s and 1990s clearly indicate that "big ticket," high-technology items, such as coronary artery bypass grafting, are of growing importance.

The complex factors related to the development and diffusion of medical devices have recently been carefully analyzed by Foote,[34] who notes the federal policies, such as funding for research through the National Institutes of Health, that promoted their development, as well as those that may retard them, such as Food and Drug Administration regulation. The same is true for health care financing policies that may either promote (Medicare, Medicaid) or retard (HCFA hospital prospective payment) the diffusion of technology. In contrast to Canada and many European countries, which place far more restrictions on the deployment of new technologies, particularly big ticket items, there is little connection in the United States between policies that promote and those that retard this development and diffusion, and no overall policy is in place related to medical technology. Furthermore, in the United States there are few constraints on the ability of providers to offer new technologies, so it is commonly the case that excess capacity develops with attendant incentives to increase use.

Administrative Costs

Administrative costs have been the focus of considerable interest and complaint but not a large amount of careful research. These include the costs of claims processing to pay physician and hospital bills, marketing, enrollment, and eligibility determination, including risk profiling. A particularly difficult problem is posed for small businesses: health insurance premiums are higher because of administrative costs that can be as much as 35% greater than those for large employers with the same coverage.[14] In addition, in their effort to contain costs through constraining use, payers have developed extensive review and authorization programs, further adding to administrative costs. Not only are administrative costs high for third-party payers, but costs of administration must be borne by hospitals, nursing homes, physicians, and consumers.

It has been estimated that administrative costs account for about 25% of the $738 billion health care expenditures in 1991.[35] Estimated savings in administrative costs for various health care reform proposals range from $31 billion[36] to $67 billion[37] or even $100 billion for single-payer systems.[35]

Unnecessary Care and Defensive Medicine

Growing attention in recent years has been focused on the potential importance of unnecessary care, including defensive medicine, in rising health care costs.[3] Whereas some care may be deemed unnecessary or inappropriate on retrospective review, it is difficult to make such a judgment at the time the care is provided. The existence of uncertainty in clinical decision making has always been recognized, but it has long been thought to be a random occurrence with few economic or policy implications. Studies in the early 1970s, however, showed wide variation among adjacent communities in Vermont and other New England states in the population-based admission rates for such elective procedures as tonsillectomy and hysterectomy.[38,39] Later studies showed marked differences in patterns of use and the costs of care in Boston, Massachusetts, and New Haven, Connecticut,[40] with no apparent differences in mortality between the two cities. A major factor, in Wennberg's view, has been uncertainty about outcomes of care and the fact that practice styles and patterns of practice vary idiosyncratically from one community to another.[41] Additional evidence regarding inappropriate or unnecessary care has come from the work of Chassin and associates.[42,43] Their studies suggest that for some procedures the application to specific clinical situations may be inappropriate as much as a third of the time.

It is difficult to estimate the effect of malpractice on defensive medicine and the cost of health care. In a study reported in 1987, Reynolds and co-workers estimated that the costs of defensive medicine were more than 3.5 times the cost of malpractice insurance premium increases.[44] They estimated the component of physician cost related to professional liability, including defensive medicine, using two different methods and found these costs were about 15% of the total cost of physicians' services in 1984. Of these professional liability costs, $3 billion was spent on insurance premiums and $100 million on settling claims not covered by insurance. Practice changes prompted by the risk of claims account for the rest. A 1991 study estimated that between 1982 and 1989, about 1% per year has been added to expenditures for physician services as a result of the professional liability system. The authors concluded that 30% of professional liability costs went to the direct payment of malpractice premiums, whereas 70% was attributable to practicing defensive medicine.[45]

Patient Complexity

Patient complexity is recognized as a factor of importance in the cost of care, particularly for low-birth-weight infants; older persons with multiple chronic diseases and disabilities; patients infected with the human immunodeficiency virus or AIDS, particularly those with numerous infections, including drug-resistant tuberculosis; trauma patients with multiple injuries associated with the growing wave of violence; and patients requiring such major procedures as heart, lung, and liver transplants. It is evident to most clinicians that because of the rapid increase in ambulatory and hospital outpatient services,[46] patients are coming to the hospital with more complex and difficult problems. Although these factors are important clinically and affect increases in hospital costs, they are not a major factor in overall cost increases because the less complicated segment of patients is being treated in less costly settings.

Excess Capacity

The issue of excess capacity is yet to be seriously addressed by policymakers, but it is likely to become more and

more important. Excess capacity is evident in some areas, such as in the number of hospital beds and the availability of medical technologies. Statewide hospital occupancy rates in 1988 were as low as 49% in Alaska, 52% in Wyoming, and 55% in Louisiana, Nebraska, and Texas.[47] Nationwide, one in three hospital beds has been empty since 1985, as hospital occupancy rates have dropped below 65%. Recent work by Fisher and associates, using the techniques of small area analysis, estimated savings in Oregon of as much as $50 million if the hospital bed supply were reduced.[48]

The current supply of physicians is also in excess of what is needed, and there is certainly a maldistribution by specialty and geographic area. Most of the imbalance by medical specialty has resulted from a rapid growth in surgical specialties and medical subspecialties. A projection of the supply of physicians by specialty for 1990 showed shortages in the 5 specialties of child psychiatry, physical medicine, emergency medicine, preventive medicine, and psychiatry and an oversupply in 16, with cardiology, endocrinology, neurosurgery, and pulmonary showing the greatest surpluses.[49] More recently, both the Council of Graduate Medical Education[50] and the Bureau of Health Professions[51] reported a physician surplus, although persistent problems of maldistribution, both by specialty and by geography, continue to leave some areas underserved. Data on the distribution of physicians show extreme variations by geographic area. The federal government designates 2,143 areas as health professional shortage areas,[52] the major criterion being defined by physician-to-population ratios. Not everyone agrees with this assessment of the physician supply problem, however. Schwartz and colleagues, for example, suggest that the increasing supply of physicians is leading to an outward movement by specialists to smaller communities, narrowing the maldistribution problem.[53]

Physician supply has increased rapidly since the mid-1960s when federal and state policies were implemented to increase medical student enrollments and expand physician supply. Total, nonfederal patient care physicians per 100,000 population increased from 125 in 1965 to 193 in 1989. The United States now has more physicians per capita than almost all other nations. Exceptions include Israel, Belgium, West Germany, and the former Soviet Union.[54] It is expected that this number will continue to increase. This oversupply has important implications for health care costs. A study by Grumbach and Lee suggests that projected costs for physician services in the year 2000, given projections about physician supply, could be as much as $40 billion in additional costs.[55]

Schwartz and co-workers, however, argue that the demand for physician services will continue to expand rapidly because of the aging of the population, the development of new diseases, and the increasing array of technically sophisticated medical services. These trends, they argue, will lead to a shortage of physicians, not a surplus.[56]

Productivity

Assessing productivity in medical care is important, but conventional measures of productivity are inherently limited. Productivity is usually defined in terms of output per labor hour, and industry typically attempts to increase productivity by substituting new machinery for workers. The service and cognitive aspects of medical care make it difficult to achieve productivity increases in this manner, although some opportunities do exist. Changes ranging from laparoscopic surgical procedures to computerized billing systems can reduce labor input. In some instances, productivity increases are not well measured in conventional statistics. For example, as hospital lengths of stay have fallen, nursing hours per patient-day have increased (suggesting falling productivity) and nursing hours per admission have fallen (suggesting rising productivity).

Health care professionals increasingly look to broader measures of productivity by redefining the unit of output. Based on the concept that avoiding errors is less expensive than fixing them, the "total quality management" and "continuous quality improvement" movements are focused on enhancing both quality and productivity. From a population perspective, the greatest productivity improvements are likely to come from two areas: increased prevention of illness and reduced use of marginally effective interventions.

Health Care Reforms—Setting the Stage

During the past 20 years, and particularly in the past decade, actions have been taken by the private and public sectors to slow the rate of increase in health care costs. Considerably less has been done to expand health insurance coverage to uninsured persons. Beginning in 1984, however, Congress has mandated incremental changes in Medicaid eligibility. This legislation, culminating with the Omnibus Budget Reconciliation acts of 1989 and 1990, required all states to establish minimum Medicaid income eligibility thresholds at 133% of the poverty level for children younger than 6 and then to phase in coverage, one year at a time, for children ages 18 and younger.[57] Several states have taken limited additional actions in an attempt to increase access for the uninsured.[58] Minnesota recently enacted a major reform proposal to cover uninsured persons,[9] and Vermont passed legislation to set in motion a plan for statewide health care coverage by 1995 (F. Butterfield, "Universal Health Care Plan Is Goal of Law in Vermont," *The New York Times*, May 12, 1992, p A12). Several other states are likely to enact reform proposals in 1992.

The first major federal attempt to contain Medicare costs was the "prospective payment system" for hospitals, passed in 1983 and implemented in the mid-1980s. It had two important effects, one intended and one unintended. As intended, expenditures for Part A (hospital services) slowed notably relative to previous trends.[59] An unintended consequence of the fixed payments, however, was that hospitals were no longer able to cross-subsidize uninsured patients through cost reimbursement with paying patients. This difficulty was exacerbated by the growth of contracting with hospitals by Medicaid programs, particularly Medi-Cal in California,[60] and preferred provider organizations and insurers. The spread of fixed-payment arrangements and contracts by payers unwilling to cross-subsidize led to rapid increases in charges (list prices) paid by the shrinking pool of conventionally insured. This, in turn, has forced up the premiums for small group enrollees—large groups typically have the power to negotiate discounts—and often to a loss of coverage. It has also deprived hospitals of implicit subsidies, which had been used for uncompensated care, adding to hospitals' financial stress and an increasing reliance on public facilities to provide care for uninsured persons.

The second major step by the federal government to curtail Medicare expenditures began in 1984, when Congress

froze physician payments in the Medicare program. Congress followed by reducing payments for overvalued procedures, including many surgical and imaging procedures, limiting charges by physicians above the Medicare allowed charge—the Maximum Actual Allowable Charge program—and establishing the participating physician and provider program. These efforts culminated in 1989 with the enactment of the comprehensive Medicare physician payment reforms, including establishment of the Medicare fee schedule, limits on balance billing, and volume performance standards.[61-63]

Following implementation of the Medicare fee schedule on January 1, 1992, many private payers began to consider applying a fee schedule based on the Medicare relative value scale but with a different conversion factor. How widespread this will become remains to be seen.

In the private sector, actions have been taken by self-insured employers and by commercial and nonprofit insurance companies. In their attempt to control costs, employers have emphasized competitive market-based strategies. These include shifting costs to employees through co-payments, deductibles, and increased premium costs; reducing benefits, sometimes eliminating coverage for dependents; cost management, including utilization review, concurrent review, preadmission or preprocedure certification, and case management; managed competition; and selective contracting.[64] Many of these approaches have affected practicing physicians, adding to what has been called the "hassle factor."[65]

In response, physician groups, including the California Medical Association, have proposed major initiatives to extend health insurance coverage universally. Many of these proposals have called for employer-mandated health insurance and an expansion of Medicaid to cover the unemployed and unemployable younger than 65.[11] The Physicians for a National Health Program proposal suggests a more basic restructuring of the way health care is financed, proposing a single, comprehensive public insurance program.[66]

To help assess the various proposals for health care reform, THE WESTERN JOURNAL OF MEDICINE will carry a series of articles during the coming year. Included will be a review of the major reform alternatives under consideration at the federal level. There will also be a discussion of the interest groups involved and their attempts to influence the outcome of the debate. Articles will follow on structural issues, such as administrative costs and eligibility, that must be dealt with by all the proposals; quality of care, emphasizing the use of tools available to physicians, such as practice guidelines and profiling, that may be useful in providing appropriate, cost-effective care; managed care; data requirements and systems; and finally a review and summary of the prospects for reform. The intent of this series is to help the journal's readers go beyond the rhetoric in which various proposals are couched and to allow a rational assessment of the strengths and weaknesses of various approaches. As this and other articles in the series will show, the problems of the health care system arise from a combination of social, legal, historical, political, and technologic factors. Simple solutions are unlikely to work, but the prospect of important changes has energized the policy debate.

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Editorials

Health Care Reform—Another View

HEALTH. Health care. Access to health care. Access to health care for all. Access to good health care for all.*

Now is the time.

What will it take?

It will take accepting limits. Although we can do many things for patients, we cannot do everything. Bodies and souls cannot always be fixed. Genetic damage, abuse of some sort, bad luck, our own lack of knowledge and technology, or, simply, error can devastate. Perfection may be our preference, but it is an unattainable and unaffordable luxury. As we acknowledge limits, and as we let the public know that medicine has limits, expectations and costs should decrease. I suspect that "accepting limits" will mean that everyone, physicians and patients and all other participants in health, will give up something so that everyone can get something.

What else will it take to establish good access to good care? We will save time and energy by eschewing the temptation to blame and to criticize. There is no reason to blame the villain who caused the current state of affairs; there is no villain.

It will also take respecting the public and regaining its respect and trust. If physicians are to play an important part in planning for improved access—and we must—we will listen carefully. As individuals and organizations, we will act as an honored profession, not as a special interest. We will speak up on behalf of patients for, if we do not, who will? The public holds in high regard those who serve it well. Our ability to affect the difficult decisions ahead depends heavily on public trust.

It will take hard work to prevent disease and damage, pain and suffering.

Finally, lest we forget, Justice Louis D. Brandeis wrote,

> A profession is an occupation for which the necessary preliminary training is intellectual in character, involving knowledge and to some extent learning, as distinguished from mere skill. It is an occupation which is pursued largely for others and not merely for one's self.[1(p2)]

Science is our particular intellectual underpinning. As we restore and heal our profession and remember what our profession is about, we need to teach. We need to teach ourselves and our students about excellence. We need to teach the public, patients, and families about risks, responsibilities, choices, benefits, limits, about staying healthy and getting healthy.

Knowing what it takes, we need to describe good health care for all. It should be

- Compassionate
- Culturally acceptable
- Convenient
- Reasonable and appropriate, indeed, excellent
- Comprehensive. Care should range from preventive through acute to rehabilitative, including care for individuals and families and communities, including care for the psyche and soma;
- Based on continued, enhanced basic and applied research. We need to know more about molecular biology, organ systems, and behavior; about growth and aging; about women and men; about ways to prevent harm.

What elements will be necessary in the newly forming, newly reforming health care system?

- We need more primary care professionals—physicians, nurses, community workers.
- We need quality assurance by education, not search and destroy. Quality assurance needs to be managed by the profession and not as a for-profit enterprise.
- The system should function smoothly for patients and physicians. This means that forms should be simple. Payment, reviews, and appeals should be fair and fast.
- There should be incentives for patients and physicians to use the system wisely.
- The structure should be flexible and not monolithic. We need to take into account geography, gender, patient needs, health professional availability, special circumstances, and special opportunities.
- There should be joint involvement, joint management, and joint ability to affect the system by all participants: patients, families, physicians, payers, hospitals and other health facilities, pharmaceutical companies, policymakers.
- It is essential to rethink the fundamentals of professional liability. The emphasis should be on healing. While we are reforming, we need to reform Workers' Compensation, a system that means well and usually does well but has been justifiably criticized for sometimes downright dishonest practices by attorneys, physicians, and patients.

Any discussion of the foundation, function, and form of our health system needs to iterate values commonly held in the United States. In 1776, Thomas Jefferson set forth our inalienable rights of "life, liberty, and the pursuit of happiness."[2] To secure these rights requires vigor and enthusiasm. Working together, moving ahead, we can renew the optimism that fuels progress. Fairness and evenhandedness are also important to all of us, as is paying attention to the vulnerable among us. Our profession has its own values. William Osler said, "Do the kind thing and do it first."[3(p178)] We also affirm altruism and provide ethical care. Arnold Relman, editor emeritus of the *New England Journal of Medicine*, wrote recently, "From its earliest origins the profession of medicine has steadfastly held that physicians' responsibility to their patients takes precedence over their economic interests (A. S. Relman, "What Market Values Are Doing to Medicine," *Atlantic Monthly*, March 1992, p 99). Now, however, "At every turn in the road physicians both in practice and in academic institutions are being attracted by financial arrangements that can compromise their professional independence (Relman, *Atlantic Monthly*, March 1992, p 105). If "caveat emptor" gets the upper hand and undermines trust, "tincture of physician" as a main element of healing is doomed.

What else will it take to establish access to good health care for all? We will need to experiment. We will need to ensure fiscal soundness. We will also need to attend to issues that may seem more social than medical: drugs, guns, violence, poor nutrition and housing, and long-term care. We will need to harness the energy we have, driven by the shared conviction that Americans deserve to have good health and

*See "Costs and Coverage—Pressures Toward Health Care Reform," by P. R. Lee, D. Soffel, and H. S. Luft on pages 576-583 of this issue.

good health care and by the awareness that health care spending is sapping our country of vitality and options.

We do have limits. We also have remarkable abilities to heal. We need to claim, to proclaim, to reclaim the basics—science, education, respect, and trust.

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Getting Some Breathing Room—Persuading Patients to Stop Smoking

ABOUT 35 YEARS AGO when I was participating in a summer internship in chronic disease research methods sponsored by the California State Health Department, a discussion took place about how to "prove" that cigarette smoking was responsible for the development of chronic obstructive pulmonary disease (COPD). Randomized controlled clinical trials were relatively new, and concerns ranged from whether there were sufficient data to suggest that any controlled trial was necessary to whether any trial was ethical. Could one, with what was known at that time, ethically randomly assign consenting adults to take up smoking or not provide all patients with the contradicting information that smoking was or, as some suggested at that time, was not harmful? Little was said or known about how difficult it was to actually get subjects to stop smoking. Most of the studies of that era related to highly motivated people who had just suffered a major illness—mostly men with stomach ulcers or myocardial infarctions. Primary prevention was rarely mentioned.

In one sense Browner and co-workers in their report elsewhere in this issue of the journal have attempted, using data from the Multiple Risk Factor Intervention Trial (MRFIT), to do such a study in the only way ethically possible.[1] As part of a randomized trial designed to reduce the risk of heart disease in what most would agree was a high-risk group, the investigators took advantage of data being obtained to assess heart disease to evaluate the effects of cigarette smoking cessation on the change in lung function. More than 12,800 men aged 35 to 57 years were enrolled in the MRFIT study. These men were randomly assigned to either an intensive integrated program of smoking cessation or usual care. Of those entering the trial, 6,347 were smokers for whom acceptable repeated pulmonary function measurements were obtained during the course of the trial. In general, acceptable pulmonary function data were available only for the latter half of the six-year follow-up study. Thus, the analysis was based on the change in pulmonary function as measured by the forced expiratory volume in one second (FEV_1) expressed as an annual rate of decline over two to four years. Unfortunately, for the hypothesis to be tested in terms of pulmonary function change, the subjects most susceptible to the effects of cigarette smoking (those with diagnosed chronic respiratory disease) were systematically excluded from the sample. Yet, even after excluding the group likely to be most sensitive to the effects of smoking cessation—that is, those with COPD whose pulmonary function is declining fastest[2]—the investigators interpret their findings as showing a beneficial effect of stopping smoking.

The authors are appropriately cautious in discussing the limitation of their findings; nevertheless, the results are important in adding to the evidence that, no matter when a patient stops smoking, the effect, at least in terms of nonmalignant respiratory disease, is beneficial. These results were recently summarized by the United States Surgeon General's 1990 Report entitled *The Health Benefits of Smoking Cessation.*[3] A relatively large body of evidence from cross-sectional, cohort, and interventional studies mostly indicates less morbidity and, in some cases, greater levels of pulmonary function among former smokers than among those who continue to smoke.

The pathophysiologic correlates of these epidemiologic findings support some postulated mechanisms for the measured responses. Generally, the earliest lesions found in smokers' lungs involve the small airways. When these are noted there may be no changes in pulmonary function as measured with the FEV_1. Changes in mucus production, however, brought about by the direct irritant effects of cigarette smoke on goblet cells in the larger airways, may result in partial obstruction, which will reduce the FEV_1. In fact, it is this mucous hypersecretion that is initially affected by a reduced exposure to cigarette smoke, with the subsequent decline in goblet cell number and a reduced production of mucus.

In humans the effect of reduced smoking on the production of mucus can be measured by reduced sputum volumes both in general population samples and in those with chronic bronchitis. A corresponding improvement in pulmonary function in patients with severe COPD can be detected within three months of stopping smoking.[4] Similarly, in normal populations (adjusted for pack-years of smoking), an improvement of about 5% in the FEV_1 is noted in both men and women after three years of smoking cessation (the interval between measurements). As long as the subjects continue not to smoke, they maintain that 5% difference from those who continue to smoke.[5] Some studies have found a reduced rate of decline in the FEV_1 in former smokers; others have found that, once the initial improvement has occurred, the decline continues at a rate similar to that in current smokers. Although it is clear that the initial improvement is maintained, few studies to date have been carried out long enough to show with certainty that, once the initial improvement is taken into account, further slowing of the rate of decline in the FEV_1 occurs. Without detracting from the importance of the MRFIT findings, I should note that the study suffers from this same difficulty of not having observed the patients long enough to be certain that the effect on the FEV_1 is not all due to the immediate effect of stopping smoking rather than an ongoing slowing of the rate of decline.

As previously mentioned, the Surgeon General's report on the health benefits of stopping smoking refers to several studies, contributing to a similar conclusion that for nonmalignant respiratory diseases, stopping smoking is beneficial. In addition, that same volume reports on a wide body of data that speak to a variety of health benefits of quitting smoking that extend beyond concerns related to the development of COPD. As indicated by the Surgeon General, "Cigarette smoking is the most important preventable cause of death in our society . . . and is responsible for approximately 390,000 deaths each year in the United States, or more than one of every six deaths."[3] Such statistics, in fact, do not consider all the effects related to smoking.

Thus, the public health message is clear. Given that more than 60% of the adult population in the United States has smoked at some time, efforts to help people stop smoking and to remain nonsmokers will have a significant impact on the health of the nation. It is imperative that primary care professionals play a vital role in this effort and have accurate information on what can be expected in smoking patients. Their smoking patients will need objective evidence beyond "the statistics" that giving up smoking will have an affect on them. Thus, if pulmonary function is measured as part of the cessation plan both before and several months after quitting, that improvement will be manifest. Because pulmonary function is a strong predictor of morbidity and mortality not only from COPD but also from cardiovascular diseases, practitioners can honestly tell patients that smoking cessation and the consequent improved lung function will lessen their risk.

Clearly, taking the time to explain to patients the importance of stopping smoking will reduce the time available to give to other sick patients in the waiting room. But because as many as 20% of the patients are there because of smoking-related conditions, an effective campaign would surely make all of our work a little easier. The potential of such a campaign to reduce costs to the national health care system would give us all (including our patients) a little more breathing room.

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Caffeine Under Examination—A Passing Grade

During the past few decades, biomedical researchers have studied caffeine more intensively than almost any other substance, naturally occurring or synthetic. Yet, when all the data have been analyzed, caffeine seems to be remarkably safe when used at current levels of consumption. In clinical research, interest in caffeine has generally been focused on coffee, with tea and caffeine-containing soft drinks receiving considerably less attention.

Why are medical investigators so attracted to research on coffee? Unlike a synthetic drug, coffee is relatively easy to study from an ethical point of view. Most people drink coffee, and administering or withholding it does not raise important ethical issues. There is also considerable interest in coffee among both the general public and the scientific community. As a consequence, investigators can initiate studies on coffee secure in the knowledge that scientific journals will welcome their findings, be they negative or positive.

Despite extensive study, misconceptions about coffee prevail among health care practitioners. When questioned on their beliefs, physicians will generally agree that coffee increases the heart rate, causes cardiac arrhythmias, elevates the blood pressure, increases sympathetic nervous system activity, and is associated with a higher incidence of coronary heart disease. The available literature as reviewed by Chou in the current issue of this journal does not substantiate any of these beliefs, however.[1] Although it is true that the ingestion of coffee or caffeine initially causes a small increase in blood pressure (with a slight reduction in heart rate) and an increase in plasma catecholamine levels, tolerance develops rapidly, and these effects disappear after a few days of regular coffee use.

So why do people continue to take a dim view of coffee? One reason is that clinical studies, mostly of a case-control design, have frequently reported its use to be harmful. On the other hand, tea has escaped any association with human disease, implying that coffee contains something other than caffeine to account for its apparent adverse effects. But a search for other potentially harmful ingredients in coffee has failed to explain the differences reported between tea and coffee.

It is conceivable that coffee may only be a marker for disease and may not be the actual offending agent. Chou and others have noted that regular coffee drinkers possess other risky life-style traits, including cigarette smoking, poor dietary habits, high stress, and greater alcohol use.[1,2] In contrast, tea drinkers are often portrayed as quietly sipping tea to relax and take a break from life's hectic pace. When coronary risk factors are examined,[3] the habits of tea drinkers are generally the opposite of coffee drinkers. Unless such differences are taken into account in the design of studies, coffee may be erroneously implicated in the pathogenesis of a variety of conditions including cancer and coronary artery disease.

For example, coffee drinking and cigarette smoking have both been associated with an increased incidence of coronary heart disease.[4-6] Most of the findings linking coffee to coronary heart disease, however, come from case-control studies.[7] In matching coronary artery disease patients to controls, researchers attempt to adjust the data analysis for other coronary risk factors. But not all risk factors can be quantitated precisely, and atherogenic behavior common to heavy coffee users may lead to potentially biased results. Thus, if respondents underestimate their cigarette use, then any residual risk of coronary artery disease from smoking may be attributed to coffee consumption. Unfortunately, small "statistically significant" increases in risk (odds ratios $<2:1$) tend to be widely reported by the media and are often portrayed as proving causation.

Longitudinal studies are less susceptible to bias from confounding variables than those using a case-control design. As noted by Chou, none of six recently reported longitudinal studies found any association between coffee use and pancreatic carcinoma.[1] Similarly, a recently completed meta-analysis of longitudinal studies found no link between coffee consumption and coronary artery disease.[7]

Coffee may not be everyone's favorite drink. It may cause some people to feel jittery and nervous, and others may have trouble sleeping when they drink coffee in the evening. We should be careful to keep our concerns about coffee in perspective, however, and avoid linking its use to perceived

sequelae not supported by scientific study. If not, we may unintentionally mislead our patients by diverting attention away from truly harmful life-style traits. Imagine a patient with coronary artery disease experiencing a sense of accomplishment after restricting coffee use while continuing to smoke and to enjoy high-fat food.

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Urinary Tract Infections—Navigating Complex Currents

Row, brothers, row! the stream runs fast,
The rapids are near, and the daylight's past!

THOMAS MOORE, 1806

SIMPLY DEFINED, urinary tract infection (UTI) refers to the presence of a substantial number of bacteria in the urine.[1] The goals of treatment and management also are simple: to relieve acute symptoms, to avert irreversible damage to structures of the urinary tract, and to prevent recurrent infections.[2] Such apparent simplicity, however belies the complexity of decisions that await a clinician who suspects this disease in an infant or child.

Much of the complexity is inherent in pediatric patients in whom symptoms are often nonspecific and variable, the collection of an uncontaminated urine specimen is frequently problematic, guidelines for treatment vary with age, and the risk of permanent damage to the developing renal system presents a serious concern. Infections of the urinary tract during childhood are second in prevalence only to infections of the respiratory tract. Fortunately, the consequences of UTI during infancy and childhood are usually benign; nevertheless, serious sequelae can occur when underlying abnormalities are not detected and appropriately managed.

In this issue of the journal, Zelikovic and colleagues provide a thorough review of the many facets of UTI in children.[3] The scope of this update reflects the complexity of the problem. Although the decision process confronting a practitioner may seem daunting, a clear understanding of the goals and guiding principles of management helps to simplify the process and avoid pitfalls that complicate diagnosis and management. We highlight selective points here.

• Consider UTI in the evaluation of any febrile infant or child. In a recent prospective study of 442 febrile infants younger than 8 weeks, 33 (7.5%) had UTIs. Of these 33 infants, urinalysis was recorded for 32; only 16 of these urinalyses were suggestive of a UTI based on the presence of bacteria or greater than 5 leukocytes per high-power field.[4] Thus, more than half of the UTIs in this population would have been undetected if the decision to obtain a urine culture were based on abnormal results of a urinalysis.

Although many ancillary tests are available and helpful, their predictive value is poorly defined. Urine culture therefore remains the gold standard for diagnosis. Nevertheless, do not underestimate the ease and value of in-office examination of an unspun, unstained urine specimen under 40-power microscopic lens. If bacteria and leukocytes are observed, the presumptive diagnosis is made.[2]

• Insist on proper specimen collection. This means urethral catheterization or suprapubic aspiration in infants and clean, midstream "catch" in older patients who are able to cooperate. A "bagged" urine specimen, the microbiologic equivalent of a heel-stick specimen for blood culture, is useful only when there are no abnormalities. Remember that the result of such a culture will not be known until after empiric therapy has begun; thus, the interpretation of a subsequent confirmatory culture will be complicated.

• Applying the strict definition of UTI based on the number of colony-forming units (CFU) of bacteria isolated per milliliter of urine must be coupled with common-sense clinical judgment. Bacterial counts can be lower in a patient who is excessively hydrated, who has had antimicrobial therapy, and who has been voiding frequently. Furthermore, the widely accepted standard definition of 10^5 or more CFU of bacteria per milliliter of urine is based on studies done in the 1950s of adult women.[5] In a remarkable study reported in 1982, 187 women with acute dysuria underwent suprapubic aspiration or urethral catheterization from which the specimen was cultured and the results compared with those of a midstream urine specimen; 47 of 98 women (49%) whose bladder urine contained coliforms had midstream urine coliform counts of less than 10^5 CFU per ml, and 30% had less than 10^4 CFU per ml.[6]

• Treatment recommendations differ depending on the infecting organism, the locus of infection, and the patient's age. The guidelines discussed by Zelikovic and co-workers are appropriate and widely accepted.[3] Discussion and controversy regarding the issue of short-course therapy for UTI in children are certain to continue. Although studies have demonstrated that bacteriologic cure rates are similar for single-dose and multidose regimens in the treatment of acute uncomplicated UTI, some have shown that the recurrence rate after single-dose treatment is higher compared with conventional regimens. For example, in a study that evaluated the efficacy of three treatment regimens using a combination of trimethoprim and sulfamethoxazole (1 dose, 3 days, and 7 days) for children with acute uncomplicated UTI, 20.5% of those given one-dose treatment had recurrent UTI compared with 5.6% and 8% of those given three days and seven days of treatment, respectively.[7]

• Appropriate imaging studies of the urinary tract should be done after the first episode of UTI in girls younger than 5 years and in boys of any age, in older girls (not sexually active) with recurrent UTI, and in any child with pyelonephritis. The goal is to detect structural and functional abnormalities that may predispose the child to the development of renal scarring and its serious sequelae, including arterial hypertension and renal insufficiency. In recent years there have been substantial gains in the quality and quantity of imaging studies. Especially notable are the proliferation of

radionuclide studies and improvements in ultrasonographic equipment and operator skills.

We agree with Zelikovic and associates that the choice of examinations depends on the facilities available, the skills and experience of the radiologist, and the clinical findings.[3] We also agree that the optimum initial imaging evaluation after a child's first UTI should include ultrasonographic evaluation of the kidneys (to detect scarring, abscess, or malformation) and voiding cystourethrography (to detect reflux and, in boys, anatomic abnormalities of the urethra). When appropriate radiologic facilities and expertise are available, however, note that some prefer ultrasonography and radionuclide voiding cystography as the initial studies for girls. Although radionuclide voiding cystography permits neither anatomic evaluation of the urethra nor the grading of reflux, it will detect reflux if present. An important feature is that with radionuclide cystography, the ovaries undergo exposure to only about 1/100th of the ionizing radiation of the conventional fluoroscopic voiding cystourethrogram.[8] If this radionuclide study is abnormal, further evaluation may then be indicated. Evaluation by a specialist should be strongly considered for any patient with moderate to severe reflux or notable findings of renal abnormalities.

The timing of imaging studies after the diagnosis of UTI has been the subject of considerable discussion. For a patient who has responded appropriately to treatment, some argue that several weeks should elapse before the voiding cystourethrography study because the inflammation caused by the acute infection may itself cause reflux. Others counter that the documentation of reflux, regardless of the cause, is the important goal. Although a delay may be ideal, the reality is that imaging a "captive" inpatient often provides the best assurance that the study will be completed. In any case, if imaging studies are delayed, many recommend continuing low-dose prophylactic antimicrobial treatment in the interim; this will prevent recurrent infection and avert possible renal damage until the urinary tract anatomy is defined.[2,9]

• The goal of the management of children with mild to moderate vesicoureteral reflux is the prevention of recurrent UTI while growth proceeds. Mild to moderate reflux usually resolves spontaneously with growth. We agree that repeated ultrasonographic evaluation every one to two years is indicated to follow renal growth and that radionuclide cystograms should be used to determine the resolution of reflux so that antimicrobial prophylaxis can be discontinued when appropriate.

In conclusion, infections of the urinary tract during childhood are a common occurrence requiring careful and thoughtful management by clinicians. In a recent symposium that addressed the clinical challenges posed by this diagnosis, Oski lamented that "no matter what progress we make in the area of urinary tract disease, the question of what to do with a presumed UTI is still a puzzler for the general pediatrician."[10] The thorough and lucid update of this topic by Zelikovic and colleagues is recommended reading for those who wish to be puzzled less and enlightened more.[3]

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Osmotic Shifts, Metabolic Compromise, and the Vulnerability of the Pons

In 1959, Adams, Victor, and Mancall published their landmark article on central pontine myelinolysis, a disease primarily affecting myelinated nerve fibers in the center of the basis pontis and associated clinically with flaccid quadriplegia and bulbar paresis.[1] In the original report, all four patients had chronic malnutrition of alcoholism. Hundreds of cases have since been reported, broadening the clinical spectrum to include liver and renal transplantation, severe burns, systemic and central nervous system malignancy, hyperalimentation, severe bacterial infections, acute hemorrhagic pancreatitis, and pellagra. A noteworthy feature remains: central pontine myelinolysis primarily affects patients afflicted with long-standing, severely debilitating disease rather than those with acute illness, and common to many of the chronic illnesses is severe hepatic dysfunction or nutritional deficiency.

The earliest clinical manifestation of the disorder is clouding of the mental state, ranging from obtundation and disorientation to coma. These changes most commonly reflect a generalized metabolic encephalopathy, as the clinical situation is often grave and there may be marked disturbances of electrolytes. Classically, over the next few days, complete flaccid paralysis develops of all four limbs, and the patient has severe weakness of the face and palate and an inability to chew, speak, or swallow. Bilateral corticospinal tract signs with spasticity and extensor plantar responses emerge several days later. In this state, associated with large midline lesions of the pons, the patient may be alert and relatively coherent but incapable of any response save for eye blinks and movements, a condition referred to as the "locked-in" syndrome. With more restricted lesions, other clinical manifestations including cerebellar ataxia and cranial nerve palsies may develop due to involvement of the cerebellar peduncles and cranial nerve nuclei. Extreme emotional lability, or spasmodic laughing or crying, may be seen. Behavioral abnormalities, often obscured by other clinical deficits, include restlessness, inattentiveness, agitation, and confusion. Clinically silent lesions are frequent, as the majority of lesions are small and affect only a few millimeters of the midline pontine raphe, corticopontine, or pontocerebellar fibers.

Early investigators regarded this disorder as invariably fatal, but the development of computed tomographic (CT)

scanning, and particularly magnetic resonance imaging (MRI), revealed that many patients survive and recover. Computed tomographic scanning is not as sensitive as MRI, and CT scans may be normal, especially early in the course of the disease. A symmetric, nonenhancing low-density lesion in the basis pontis without mass effect is characteristic, and the CT scan abnormality may persist long after a patient has recovered clinically. Magnetic resonance imaging typically shows a hyperintense signal in the pons on T2 images, usually sparing the periphery of the basis pontis. Small lesions may be detectable with MRI in the absence of clinical findings. Brain-stem auditory evoked potentials offer an additional diagnostic tool but are not specific for central pontine myelinolysis and do not indicate the extent of the lesion.

The lesion is unique in that the process primarily affects myelinated nerve fibers, yet spares axis cylinders and neurons in the absence of inflammation. At the center of the lesion there may be necrosis of all tissue elements. The rest of the lesion is characterized by macrophages, axonal spheroids, proliferated microglia, and reactive astrocytes and is characteristically well demarcated from the surrounding tissue. The topography of the brain lesions is distinctive in that the basis pontis is almost uniformly affected, and commonly the lesion extends symmetrically to involve the middle cerebellar peduncles, pontine tegmentum, midbrain, and, rarely, the medulla. Extension beyond the brain stem is well documented, and discrete, irregularly shaped myelinolytic foci may be symmetrically distributed in the thalamus, subthalamic nucleus, striatum, pallidum, amygdala, extreme capsule, external and internal capsules, the anterior commissure, and deep white matter of the cerebellum and cerebral cortex. In extrapontine myelinolysis, there is a particular predilection for the lateral geniculate body of the thalamus, a fact that may provide insight into the genesis of the myelinolytic lesion. The close apposition and admixture of gray and white matter, a feature found nearly exclusively in the basis pontis and lateral geniculate body, is considered by many investigators to be fundamental to the distribution of the lesions in central pontine myelinolysis. Riggs and Schochet have further proposed that the high vascularity of the gray matter, five times greater than that of white matter, may play a contributory role, perhaps because of heightened exposure of the vulnerable oligodendrocytes to the bloodstream.[2]

Theories concerning the pathogenesis of pontine myelinolysis have principally involved electrolyte disturbances and, more specifically, derangements of osmolality. The importance of osmotic shifts, first recognized in association with the rapid correction or overcorrection of hyponatremia and now more generally as an extreme osmotic stress without regard to the baseline sodium value or the source of the hyperosmolality, is becoming increasingly understood. Serum sodium is the major determinant of serum osmolality, and small fluctuations in serum sodium levels produce major changes in serum osmolality. The rapid correction of profound hyponatremia is likely to be associated with large shifts in serum osmolality and may lead to myelinolysis. The correction of hyponatremia is also one of the most common clinical situations in which large shifts in serum osmolality occur. Pronounced rises in osmolality, with resultant myelinolysis, may clearly result from the development of severe hypernatremia from a normonatremic baseline, as convincingly demonstrated in the case report of William Clark, MD, in this issue of the journal.[3] Hyperosmolality from other sources, including hyperglycemia and azotemia, with or without hypernatremia, is also a risk factor in the genesis of demyelinating lesions. Other electrolyte disturbances, such as hypomagnesemia and hypokalemia, may be contributory.

The critical role of patient susceptibility cannot be overemphasized. Extreme osmotic shifts, be it from the rapid correction of hyponatremia, acute hypernatremia, renal insufficiency, or hyperglycemia, in otherwise healthy, well-nourished persons are unlikely to be associated with the occurrence of central pontine myelinolysis. Susceptible patients typically have a long history of hepatic insufficiency of many causes including alcoholism, severe nutritional deficiency, or both. In patients suffering from fatal burns, who have a 7% incidence of demyelinating lesions, a hyperosmolar insult was sufficient to cause the disorder only if the insult occurred after a sustained period of hypercatabolism and body wasting.[4] The two elements are crucial: a metabolically compromised host and extreme osmotic stress. Recently the occurrence of myelinolysis in liver transplant recipients has been highlighted, particularly in association with the use of the immunosuppressant cyclosporine and low serum cholesterol levels. These patients uniformly have end-stage liver disease and their low serum cholesterol levels undoubtedly reflect underlying nutritional compromise. Furthermore, many liver transplant patients who develop myelinolysis experience pronounced perioperative rises in serum sodium concentrations, often in the absence of hyponatremia.[5,6] The susceptibility of metabolically compromised hosts may possibly be explained by a reduced capacity to generate adequate cerebral concentrations of organic osmolytes, notably myoinositol, taurine, and other amino acids, that serve to protect the brain from large fluctuations in osmolality.[7]

Clark's case report underscores the necessity of these two predisposing factors. He describes the case of a patient with severe hepatic insufficiency in whom central pontine myelinolysis developed in association with an episode of extreme osmotic stress. Severe hypernatremia and hyperosmolality developed in association with treatment with lactulose, an agent that induces osmotic diarrhea. In keeping with the typical clinical course of this disorder, the clinical signs developed seven days after the start of hypernatremia. The patient's dysarthria, drooling, difficulty swallowing, and marked weakness of the face and palate with quadriparesis and bilateral Babinski's signs correlate well with the central pontine signal abnormality seen on MRI. Her mutism may be a reflection of pseudobulbar palsy or may relate to the several areas of signal abnormality in the periventricular white matter.

This report provides further evidence that, in a host with metabolic compromise, pronounced changes in serum electrolytes or other osmotically active particles may be particularly damaging. To prevent pontine and extrapontine myelinolysis and their debilitating neurologic sequelae, great caution must be exercised when administering therapeutic regimens associated with fluctuations in serum osmolality.

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The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Earthquakes and the Practicing Physician

To THE EDITOR: We read with interest the recent article by Conover describing how office-based surgeons could prepare for the next Great Quake.[1] He has issued a warning that many people in California are beginning to heed, but he leaves unanswered how physicians other than office-based surgeons might contribute to the medical aspects of earthquake preparedness. In the worst-case scenario, experts predict as many as 100,000 casualties after the Great Quake.[1-4] Because many hospitals will be destroyed or rendered nonfunctional, and outside assistance will not begin to arrive for at least 72 hours,[1,4,5] it is critical that physicians and other health care personnel be prepared to provide immediate care under these austere conditions.

Fortunately, there is a program that has been in existence since 1989 in Orange County to address this problem, called Medical Disaster Response (MDR). For this program a nonprofit corporation has developed for the public benefit a plan to provide both the equipment and the training to enable volunteer physicians, nurses, and other medical professionals to provide immediate, on-scene, advanced medical care to victims of a massive earthquake. It is the only program of its kind currently available in the United States.

The plan involves a course curriculum that includes triage instruction, administering field anesthesia and analgesia, airway intervention, the management of crush injuries and amputations, and integration into the incident command system. Following didactic instruction, physicians participate in hands-on training with a computer interactive disaster simulation and a crush injury laboratory during which procedures are practiced on cadaver material.

The MDR equipment consists of critical care supplies and exists in two formats: a solo backpack and supply modules. These backpacks are issued to physicians who complete the course, and they contain sufficient supplies to treat four to six critically injured victims. Physicians keep them with them at all times, usually in the trunk of their cars. The supply modules contain enough equipment to treat 20 to 25 critically injured victims for 24 hours. These are stored within the community in such locations as schools or fire stations.

The Medical Disaster Response program is the result of seven years of research and development. To date, MDR has conducted four disaster medical director courses and trained 152 physicians, 74 nurses, and 13 allied health professionals. The first sets of modules are now in place, and 40 backpacks have been distributed to physicians, with plans under way to persuade hospitals to fill them. Ultimately 125 to 150 modules will need to be pre-positioned and 375 physicians and 1,000 nurses and other support personnel will need to be trained to cover the entire county.

Disaster planning and preparation is a complex task requiring involvement by local, state, and federal agencies. Because 90% of survivors are rescued by civilian volunteers within the first 24 hours,[6] a local plan for immediate advanced medical help for these victims is crucial to prevent the thousands of deaths that would otherwise occur. The MDR project offers all health care professionals an opportunity to change what would otherwise be a needlessly deadly event. As indicated by the recent 7.5 earthquake in Landers, California, we have no time to lose.

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Blood-Saturated Shoe Covers

To THE EDITOR: I read with interest the article by Paul Summers, MD, and colleagues in the August issue.[1] I wholly concur with the authors' conclusion that shoe covers are a possible source of blood contamination and cross-contamination. At my institution, in heavily contaminated or infected cases, surgeons are required to remove shoe covers inside the operating room before exiting into the hallway. I think that, at this time of high risk for AIDS [the acquired immunodeficiency syndrome] and hepatitis, all cases should be treated as potentially contaminated or infected. Therefore, at the end of operations, surgeons should remove shoe covers with a gloved hand before removing gowns and gloves. This precaution is of the utmost importance, not only to prevent transmission of the AIDS virus in fresh blood but also to prevent exposure to the hepatitis virus, which stays alive in dried blood for an extended time.

I congratulate the authors on presenting a most interesting and important point.

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REFERENCE

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Put Your Money Where Your Advice Is

To the Editor: As a physician, I observe the debilitating effects of tobacco and alcohol products in my patients on a daily basis. Because I give each of them my encouragement and advice in ending their addiction, I feel it would be hypocritical if my personal financial portfolio included investments in companies directly involved in the manufacture and marketing of these products. As a professor of medicine at a university medical center, I also realize that my example can encourage young health professionals to consider excluding these products from their own investments.

My university has enlisted several companies to assist them in investing for a campus-wide retirement organization. Recently this organization solicited participation by university personnel in an election for a representative to its advisory board. A total of 13 well-qualified candidates were proposed, and their biographical statements were widely distributed to the electorate. To determine each candidate's position regarding divestiture, or at least to the extent they would advise limiting the university's investments in tobacco and alcohol products, I contacted each candidate and asked the following question: "Would you divest or seek to limit the University Retirement System's investments in tobacco and/or alcohol products?" Of the 13 candidates, 10 responded.

Against Divesting	Ambivalent	For Divesting	No Commitment
1	3	5	1

I voted for the candidate I considered the best qualified and who favored divestiture. The winner was one of the five candidates for divesting.

Questioning the investment policies of those institutions to which we belong—for example, schools and medical societies—is an underused tactic for avoiding support of tobacco and alcohol companies.

JOSEPH A. ABBOTT, MD
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San Francisco, CA 94109

Let's Not Do With Euthanasia What We Did With Abortion

To the Editor: It looks as though it is coming—amid protest, fear, and warnings of Nazi-like death camps. But it is so logical, so economical, and so merciful in many cases that it appears inevitable. This fearful yet desirable apparition is, of course, euthanasia, and it is becoming the subject of hot debate.*

In The Netherlands both assisted suicide and active euthanasia are commonplace since sympathetic courts will not prosecute. In the United States, there is a growing sympathy for those suffering from painful and hopeless conditions, and we are now beginning to accept passive euthanasia to a greater extent. We aren't ready for active euthanasia yet, and the majority of doctors here still decry assisted suicide. It seems in 1992 that all this is unacceptable and remote and that it won't come to America, at least not in our lifetimes.

Let's not be too sure about that. Popular opinion has made 180-degree turns, and even our own conservative medical profession has reversed itself dramatically in our time. Before the famous *Rowe versus Wade* decision by the Supreme Court and before some states had liberalized abortion laws, the image of a physician who did abortions for anything other than to save a mother's life, or at least her health, was on a par with that of a drug dealer today. There certainly has been an almost complete reversal in our attitudes now that abortion on demand is legal. So could our rejection of active euthanasia take a similar turn.

Though I have mixed thoughts about euthanasia, I fear that, as we now have more than a million abortions each year, we could end up having millions of the sick and elderly being put to sleep. There will be all sorts of pressures to expand the indications beyond pain and misery and hopelessness. These pressures could include deficits in national and state budgets, a continued rise in health costs, overcrowding due to excess population, environmental concerns, limited resources clashing with unlimited demand, housing shortages, and more.

There is another pressure that I fear even more—that euthanasia may become a profitable specialty. Were a death well paid for, and it certainly could be, would we not see a rising number of physicians seeking to profit by it? Good pay encouraged many life-conscious obstetricians to take up abortion, and the profitability of selling one's expertise or persuasiveness in the courtroom has created a new specialty, "the hired gun." Imagine these new thanatology specialists, with their own societies and associations and their own medical journals, devoting their practices to what some altruistic doctors have always done for free. Do we want a new professional class of medical killers, and what would their true motives be, compassion or money?

There are many of us who have eased patients along with drugs, realizing we were hastening death, but we have done it out of pure compassion. We have not demanded a fee for this. This is the way it should be if euthanasia becomes legal, as I believe it must someday.

Let us insist that whosoever has a patient so in need of euthanasia that compassion screams for it, that person be compassionate enough to do it for free. This will eliminate the commercial aspects, will parry criticism, will avoid all conflict of interest, and will be truly humanitarian. I see a real danger to our society if we do not.

GEORGE B. MARKLE IV, MD
1003 N Shore Dr
Carlsbad, NM 88220

*See "Physician Aid in Dying—What Physicians Say, What Patients Say," F. J. Girsh, EdD; and the Editorial Comments by P. K. Longmore, PhD, C. K. Cassel, MD, A. R. Jonsen, PhD, and F. Fitzgerald, MD, in the August 1992 issue of The Western Journal of Medicine (Vol 157, pp 188-194).

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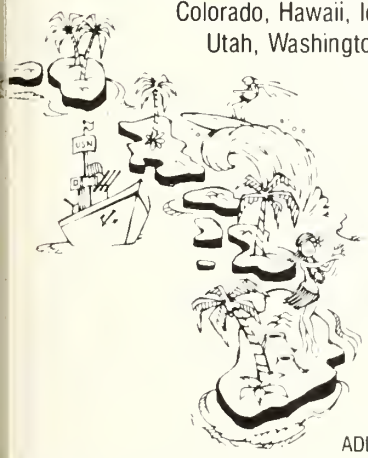

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1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

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3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

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6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

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8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

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Idaho's Department of Health and Welfare, State Hospital North, has an opportunity for a physician as Medical Director for a 75-bed adult substance abuse and psychiatric treatment hospital. Primary responsibilities include patient medical diagnosis and treatment; medical consultation; shared on-call; employee wellness and infection control. Small facility allows for progressive and innovative practice and a participative management style. Competitive salary; relocation assistance; excellent benefit package. Rural setting located at the base of the Selway-Bitterroot Wilderness Area. Experience Idaho – it's what America used to be! Contact Marvin Lambrecht, Administrator, State Hospital North, PO Box 672, Orofino, ID 83544; (208) 476-4511.

EOE/MF/HC/VET

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

SAN FRANCISCO BAY AREA. Family Practice and Fortune 500 Industrial Occupational clinic and hospital-based recovery unit needs associate in San Francisco bay area. Request BC/BE Family Practitioner or Osteopath for busy, lucrative practice in weather-prime area. Guaranteed salary and incentives. All offers considered and negotiable. Call Jenelle, (510) 680-8933.

PHYSICIANS WANTED

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Dan Hiatt in care of Tammie Johnson, 8009 S 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

MOUNTAIN VIEW. BC/BE Family Physician to join thriving four member Family Practice group located in the heart of the Silicon Valley. Practice includes Surgery and Obstetrics. C-sections are OK. Excellent salary and benefits. Contact Dianne Higgins, MD, 253 Franklin St, Mt View, CA 94041; (415) 967-5591.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

(Continued on Page 598)

(Continued from Page 597)

PHYSICIANS WANTED

THE VA MEDICAL CENTER AT SALT LAKE CITY, UTAH, is accepting applications for ACOS/Ambulatory Care. The ideal candidate would have experience in developing a comprehensive Ambulatory Care program and be Board Certified in Internal Medicine and eligible for an academic appointment at the University of Utah. The Department of Veterans Affairs offers a wide range of benefits including a tax-deferred savings plan and 30 days vacation per year for full-time physicians. Salaries are based on education, training, experience, and tenure. Salt Lake City is nestled at the foothills of the Wasatch Mountains and offers a wide range of recreational and cultural activities. The climate is moderate. Subject to random drug screening. The VA is an Equal Opportunity Employer. For additional information and application, telephone **Glenda Taylor, Human Resources Department at (801) 582-1565, Ext 1284** or write to:

VAMC (05C)
500 Foothill Blvd
Salt Lake City, UT 84148

NORTHERN CALIFORNIA

San Jose's leading multispecialty group is growing. We are seeking BC/BE physicians in the following specialties:

- Orthopedic Surgery
- Family Practice
- General Surgery
- Occupational Medicine
- ENT

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc*, 45 S. 17th St, San Jose, CA 95112; **or call (408) 282-7833.**

*An independent physician group affiliated with Stanford University Medical Center.

CALIFORNIA. Central Sierra foothills group practice is actively recruiting several Family Practitioners. Limited call, salary or guarantee, generous remuneration package with unlimited potential. OB is optional. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411, or FAX (415) 399-0411.

CALIFORNIA–MONTEREY BAY. ENT. Solo ENT, beginning fellowship January 1993, seeks one year coverage by physician of same specialty. Fully equipped hi-tech office located in exclusive medical complex. Excellent partnership opportunity. Mild climate enhances coastal exploration. Call (408) 459-9656 and send CV and inquiries to PO Box 2571, Santa Cruz, CA 95063-2571.

FAMILY PRACTICE. Practice in the world famous Napa Valley grape growing region, 90 minutes north of San Francisco. Established group of three physicians has an opening due to a retirement. Competitive income guarantee, coverage and privileges at esteemed 160-bed hospital. Call Anders Karlman, Karlman Associates, 1118 Pine St, Ste 124, St Helena, CA 94574; (800) 634-3561, FAX (707) 963-2769.

PRIMARY CARE IN THE PACIFIC NORTHWEST. Diverse opportunities for Family Physicians in urban and rural health centers throughout Washington, Oregon, Idaho, and Alaska. Loan repayment possible. Practice where it's nearly perfect. Send CV to Sarena Seifer, MD, Northwest Regional Primary Care Association, 4154 California Ave, SW, #7, Seattle, WA 98116; (206) 932-2133.

HAWAII. FAMILY PRACTITIONER WITH OB SKILLS needed for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Puanani Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792. (808) 696-7081.

ASSOCIATE DEAN AND PROGRAM DIRECTOR. UNIVERSITY OF WYOMING FAMILY PRACTICE RESIDENCY PROGRAM AT CASPER. The Associate Dean and Program Director at the University of Wyoming Family Practice Residency Program at Casper oversees a well established, fully accredited program. This position carries the responsibilities of academic and administrative leadership, as well as teaching and research. Casper is centrally located in the state and is home to the Wyoming Medical Center, the affiliated hospital for the program, and the major medical referral center for the state. Casper offers the advantages of living in a small city that lacks the usual urban problems in an area that offers four season recreational activities. Minimum qualifications include a Doctor of Medicine degree from an approved US college of medicine; BC in Family Practice; eligibility for licensure in the state of Wyoming; and hospital staff privileges at the Wyoming Medical Center, including Obstetrical privileges. A background in Family Practice education, research, and academic administration is also required. The successful candidate should have strong interpersonal and organizational skills. Please send a cover letter of application, a CV, and the names and addresses of three references to Joseph F. Steiner, PharmD, Chairman, Associate Dean Search Committee, University of Wyoming, Family Practice Residency Program at Casper, 1522 E. A St, Casper, WY 82601. The University of Wyoming is an equal opportunity, affirmative action employer.

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CONTACT: Colleen Mooney

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TWO BC/BE OB/GYNs with commitment to caring for the underserved, needed to join 13 physician (OB, Family Practice, Pediatrics, Internal Medicine), Primary Care community health clinic in Toppenish and Grandview, Washington, which has a four physician team (Family Practice, OB, Internal Medicine). Rural setting, beautiful sunny central Washington near Columbia River Gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

CENTRAL OREGON. Progressive, financially stable rural hospital seeks a qualified physician for weekend Emergency Department coverage. Full-time, benefits eligible employment opportunity. New emergency/ancillary services wing. Call Don Ptacnik, Mountain View Hospital District, (503) 475-3882.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

(Continued on Page 599)

(Continued from Page 598)

PHYSICIANS WANTED

NORTHWEST REGION

Physicians needed to join a multispecialty group, partnership, or solo practice, due to the explosive population growth. BC/BE physician specialties:

- FAMILY PRACTICE
- PEDIATRICS
- CARDIOLOGY
- PSYCHIATRY
- INTERNAL MEDICINE
- ORTHOPEDICS

Excellent practice opportunities offer guaranteed income and a strong referral base.

Contact with CV to:

Kevin Malee, Healthcare Specialist
INLAND EMPIRE PERSONNEL SERVICE
BECKER' PHYSICIAN PLACEMENT
4407 N Division, Ste 500
Spokane, WA 99207
(800) 945-4066/FAX (509) 484-6317

NORTHERN CALIFORNIA. Opportunities available with Comprehensive Medical Evaluations in Sacramento and San Jose for BC physicians in Orthopedic Surgery, Psychiatry, Internal Medicine, and subspecialties, Dermatology, Neurology, Physical Medicine/ Rehabilitation, Ophthalmology, Otolaryngology, Plastic/Reconstructive Surgery and Toxicology/ Occupational Medicine, to perform forensic medical evaluations. This is an excellent opportunity to supplement income without increasing your practice overhead. Send inquiry to Terence Doyle, Comprehensive Medical Evaluations, 87 Scripps Dr, Ste 308, Sacramento, CA 95825; or call (916) 567-3411.

NEVADA–GASTROENTEROLOGIST. BC/BE needed to join General Intern practice in southern Nevada. Generous salary leading to full partnership. Interest in Internal Medicine preferred. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

PALO ALTO MEDICAL CLINIC, a 150 physician multispecialty group with a national reputation for innovation and excellence, seeks BC Family Practice or Emergency Medicine physicians for full-time practice in Urgent Care facility. Occupational Medicine experience desirable. Competitive salary based on experience. Excellent benefits package. Two year partnership track. Please forward letter of interest and CV to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

SAN DIEGO AREA. Internist and/or Cardiologist, Pulmonologist, BC/BE, to join busy Internal Medicine/subspecialty group. Excellent income opportunity. Well-equipped office across from hospital. Send CV to Box 250, 647 E St, Chula Vista, CA 91910.

FAMILY PHYSICIAN OR INTERNIST to join six physician practice in lovely coastal community 25 miles south of San Francisco. Flexible schedule. CV to Dr Larry Casalino, Coastside Medical Clinic, 225 S Cabrillo Highway, Half Moon Bay, CA 94019.

PEDIATRICIANS – Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

(Continued on Page 600)

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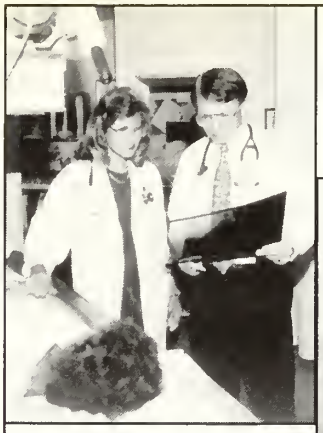

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Arizona: CIGNA Healthplan, Professional Staffing, 11001 N. Black Canyon Hwy, Suite 400-49, Phoenix, AZ 85029, (800) 252-2471.

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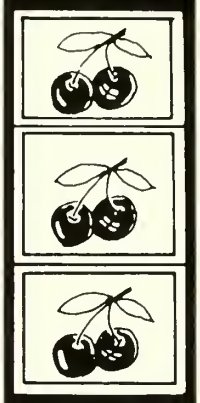

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(Continued from Page 599)

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San Ramon, CA 94583
PHONE: (510) 833-0190
(800) 824-9811
FAX: (510) 833-9290

NEW MEXICO! FHP. One of America's most progressive HMOs, is seeking a BC/BE Internist to join its 28 member group in Albuquerque (population 500,000). You'll enjoy big city advantages plus small town friendliness. Deliver in/outpatient care in well-equipped, modern facilities. Emphasis on quality care, personalized patient services. Guaranteed salary, generous retirement, malpractice and comprehensive benefits provided. Contact Mary Consie, (800) 444-4347, or write FHP, 4300 San Mateo NE, Albuquerque, NM 87110. EOE.

PHYSICIANS WANTED

BC/BE FAMILY PRACTITIONER for satellite clinic of prestigious multispecialty group practice. Join one other Family Practitioner and one Physician's Assistant in small town setting with urban culture 20 minutes away. Generous benefit package. Send CV to Donald Benz, MD or Karen Stanton, The Vancouver Clinic, Inc, PS, 700 NE 87th Ave, Vancouver, WA 98664; (206) 254-1240.

FAMILY PRACTICE/INTERNAL MEDICINE. Three Physicians wanted for two locations (Merced, Loma Linda areas). No administration. Six-figure salary plus monthly profit sharing, malpractice (including tail) paid, other fringes. Call Mike Buker, Administrator, Medical Advantage; (209) 383-3990, or send CV to 750 W Olive Ave, Ste 104, Merced, CA 95348.

PUGET SOUND. BE/BC Family Practitioners to staff walk-in clinics affiliated with 95 physician multispecialty group, located 30 miles north of Seattle. Opportunity for exceptional personal and professional lifestyle. Position offers competitive salary with excellent benefits. Available winter 1992 and summer 1993. Send CV to J. G. Finley, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201.

BC/BE FAMILY PHYSICIAN to join three other Family Practitioners, OB/GYN, Internist, and Physician Assistant at busy Migrant/Community Clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work, and Emergency coverage. Excellent relationship with well trained BC Family Practitioners and surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation liberal. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

PHYSICIANS WANTED

Western States OPENINGS
Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SEATTLE, WASHINGTON. FAMILY PHYSICIAN BC/BE, part- or full-time, wanted for a stimulating practice in a comprehensive Primary Care community clinic serving a diverse Asian/Pacific Islander population. OB required. Cantonese language skills helpful. Contact Debra Cavinta, Administrative Assistant, International District Community Health Center, 416 Maynard Ave S, Seattle, WA 98104; (206) 461-3617. EOE. Closing date 11/30/92.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

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AIR FORCE

(Continued from Page 600)

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SCENIC COLORADO front range community of 30,000, with a strong, growing economic base, needs Family Physicians. Join a group of physicians or establish a solo practice with cross coverage. Full range of Family Medicine, including OB, available. Hospital offers generous guarantee for the physician wanting to be close to Rocky Mountain recreation as well as metropolitan areas. Call Rita Longino at (800) 279-5267, or FAX CV to (800) 467-1246, or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

HIV EARLY INTERVENTION PROGRAM needs full-time Primary Care or Internal Medicine physician to work within innovative outpatient setting. Opportunity to follow HIV-positive patients through full spectrum of care along with multidisciplinary staff. Teaching and hospital attending opportunities available. Salary and benefits are competitive and based upon experience. Contact Martin Fenstersheib, MD, Public Health Medical Services, 2220 Moorpark Ave, San Jose, CA 95128; (408) 299-5858.

OREGON. Immediate opportunities for Family Practitioners with or without Obstetrics to join busy practices in Oregon's Willamette Valley. Rural lifestyle with easy access to cities, beautiful area, great medical community and $5,000 Oregon State Tax Credit. Contact Beverly Day, Lebanon Community Hospital, Box 739, Lebanon, OR 97355; (503) 451-7110.

PHYSICIANS WANTED

IDAHO. BC Family Practitioner to join Family Practice Group (OB required) in university town of 50,000. Good benefits and competitive first year salary, then association. Interest in resident and medical student teaching. Contact Michael S. Baker, MD, 755 Hospital Wy, Ste A4, Pocatello, ID 83201; telephone (208) 233-7000.

HAWAII, CALIFORNIA, AND FLORIDA COAST clinics need Family Practitioner or Internal Medicine Physician to $110,000 plus benefits/fee paid. Share call. CV to LAM Physician Associates, Dept W, 444 Hobron Ln, #207, Honolulu, HI 96815-1229. Pat Lam, (808) 947-9815; toll-free (800) 258-4526.

SEATTLE. BC/BE GENERAL INTERNIST, part-time, to practice on Mercer Island. Join BC Internists' group with two Seattle area offices. No income guarantee; group and location excellent. Write Royce A. Morrison, MD, c/o 901 Boren Ave, Ste 1600, Seattle, WA 98104.

SAN FRANCISCO AREA. Internist/Family Practitioner, full-time or part-time. Established practice; challenge and diversity of private practice. Send CV to Martin Lorber, MD, 901 Campus Dr, Rm 208, Daly City, CA 94015; or call (415) 992-4466.

SAN FRANCISCO BAY AREA–FAMILY PRACTITIONER, PEDIATRICIAN, PSYCHIATRIST. Recently trained, energetic, enthusiastic, BC preferred, for 18 physician Palo Alto Medical Clinic satellite. Clinic is progressive 150 physician multispecialty group known for innovation and excellence. Practice is established and growing. Excellent location, convenient access to San Francisco and Stanford. Excellent compensation/benefits package. Please send CV and letter of interest to David Hooper, MD, Medical Director, Palo Alto Medical Foundation, 39500 Liberty St, Fremont, CA 94538.

PHYSICIANS WANTED

URGENT CARE/PRIMARY CARE PHYSICIANS. Current permanent positions available in Phoenix, Denver, Colorado Springs. Attractive settings with reasonable workload. Enticing locum tenens assignments available also throughout the Rocky Mountain west. Call or write Ed Novelli, Interim Physicians, 4155 E Jewell, Ste 1018, Denver, CO 80222; (800) 669-0718.

INTERNAL MEDICINE BC/BE. Full-time position in established four physician group. Excellent location on San Francisco peninsula adjoining a quality community hospital with Stanford affiliation. Senior physician planning retirement soon. Send résumé to Number 274, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNIST, BC/BE–SAN DIEGO to join well established, 10 physician Internal Medicine multispecialty group. Opportunity to take over retiring physician's Primary Care patient base. Guaranteed salary with incentive and full benefits for first year. Send CV to Mr James McKeon, Administrator, 5111 Garfield St, La Mesa, CA 91941.

NORTHERN CALIFORNIA PEDIATRICS. BC/BE Pediatrician to join three Pediatricians and two Nurse Practitioners in beautiful northern California coastal city. Competitive salary first year, then partnership if mutually agreeable. Contact C. Cody, MD, 2800 Harris St, Eureka, CA 95501; (707) 445-8416.

FAMILY PRACTITIONER to assume established practice (located in Southern California mountain resort community) purchased by multispecialty group. Send CV to Number 276, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 602)

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FHP also has opportunities available in California, Utah, New Mexico, Nevada, Guam, and Management. EOE

(Continued from Page 601)

PHYSICIANS WANTED

GENERAL INTERNIST–OREGON. BC/BE General Internist to join 21 member Internal Medicine department of 62 physician multispecialty clinic. University town. Guaranteed salary, incentive bonus, excellent benefits. Send CV to Richard M. Rytting, MD, Medical Director, The Corvallis Clinic, PC, 3680 NW Samaritan Dr, Corvallis, OR 97330.

GLENDALE, CALIFORNIA. Positions available in OB/GYN and Pediatrics. Growing Family Practice group. Immediate opportunity. Guaranteed income and growth. Send confidential CV or address inquiries to F. S. Sarkis, MD, 517-519 E Broadway, Glendale, CA 91205; telephone (818) 243-9503, FAX (818) 243-2713.

INTERNAL MEDICINE/PRIMARY CARE. BC/BE, recently trained (university program preferred) for group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

BC/BE OB/GYN AND FAMILY PRACTITIONER with commitment to caring for the underserved, needed to join one Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs and four Family Physicians. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, NHSC loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

PHYSICIANS WANTED

INTERNIST BC/BE to join 10 physician (OB, Pediatrics, Internal Medicine), Primary Care community health clinic in Toppenish, Washington serving migrant and seasonal farm workers with common as well as Third World maladies. Reasonable call schedule with 3.5 Internal Medicine department. Rural setting, beautiful, sunny central Washington near Columbia River Gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and professional liability. Contact Ann Garza, Director of Personnel, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

AMBULATORY/FAMILY PRACTICE group seeking Family Practice/General Practice physician for rapidly expanding practice in northern California. Prime recreation area in growing community of 70,000. Compensation and benefits include malpractice, health insurance, and CME. Call (916) 222-2113 or send résumé to 191 Hartnell Ave, Redding, CA 96002.

GENERAL INTERNIST AND INTERNIST/RHEUMATOLOGIST. Successful 28 member multispecialty group, fee-for-service, seeking replacements for retiring partners. Stanford Hospital affiliation with teaching opportunities. Contact T. J. Fiene, MD, Menlo Medical Clinic, 1300 Crane St, Menlo Park, CA 94025; (415) 323-8161, FAX (415) 324-9447.

TWO INVASIVE CARDIOLOGISTS AND FAMILY PHYSICIANS NEEDED. Unique opportunity. Gorgeous California central coast. Partnership within year. Send references/CV to PO Box 220, 395 Del Monte Center, Monterey, CA 93940.

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- PSYCHIATRY
- ORTHOPEDICS
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(Continued on Page 603)

(Continued from Page 602)

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Don't Forget! The deadline for submitting classifieds for the January issue of WJM is November 23. Send your advertisement to **Classified Advertising, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602; (415) 882-3376.**

(Continued on Page 604)

(Continued from Page 603)

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WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St, Anchorage 99508. (907) 562-2662. Annual Meeting: 1993, date and place to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: June 6-8, 1993, Loew's Ventana, Tucson.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1993, date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1993, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-15, 1993, Society Office, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1993, date and place to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1993, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 19-21, 1993, Jackson Lake Lodge, Moran.

ADVERTISING INDEX

AUDIO-DIGEST FOUNDATION 499

BLUE CROSS OF CALIFORNIA
California Care 506, 507

BROWNING-FERRIS INDUSTRIES
Medical Waste Systems 519

CALIFORNIA DEPARTMENT OF CORRECTIONS 597

CALIFORNIA MEDICAL ASSOCIATION
Annual Session 523

CIGNA HEALTHPLAN 599

CLASSIFIED ADVERTISING 596, 597, 598, 599, 600, 601, 602, 603, 604

CNA 526

COMPHEALTH 604

ELI LILLY & COMPANY
Humulin 505

FHP HEALTH CARE 602

450 SUTTER MEDICAL/DENTAL BUILDING
San Francisco 604

GLAXO INC.
Zantac ..... 3rd & 4th Covers

DAVID BRENT JONES GROUP 501

KAISER PERMANENTE 597

MARION MERRELL DOW
Cardizem CD 509, 510

PALISADES PHARMACEUTICALS INC.
Yacan 501

PHYSICIANS INTERINDEMNITY INSURANCE 497

ST. JOSEPH HEALTHCARE SYSTEM 600

SANDOZ PHARMACEUTICALS
DynaCirc 494, 495, 496

G.D. SEARLE & COMPANY
Calan SR 503

SUTTER NEUROSCIENCE CENTER 521

UNIVERSITY OF SOUTHERN CALIFORNIA
University Hospital 512, 513

UPJOHN COMPANY
Ragaine ..... 2nd Cover, 493

US AIR FORCE 601

THE WESTERN JOURNAL OF MEDICINE
Subscription 493
Special Issues 515
Medical Student Writing Award 593

One Of A Kind

Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within 4 weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within 1 or 2 weeks after starting therapy with Zantac 150 mg b.i.d
6. Treatment of endoscopically diagnosed **erosive esophagitis**. Healing of endoscopically diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with Zantac 150 mg q.i.d Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with Zantac.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD, and erosive esophagitis.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug

PRECAUTIONS: General: 1 Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION) Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution)

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Zantac is secreted in human milk Caution should be exercised when Zantac is administered to a nursing mother
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported Rare reports of reversible involuntary motor disturbances have been received
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d intravenously for 7 days, and in 4 of 24 subjects receiving 50

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred
Musculoskeletal: Rare reports of arthralgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 150 Tablets (ranitidine HCl equivalent to 150 mg of ranitidine) are peach, film-coated, five-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets

Zantac® 300 Tablets (ranitidine HCl equivalent to 300 mg of ranitidine) are yellow, film-coated, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine per 1 mL in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25°C (39° and 77°F). Dispense in tight, light-resistant containers as defined in the USP/NF.

May 1992
2130A

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

Zantac® 150 Tablets/Zantac® 300 Tablets:
Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

Zantac® Syrup:
Manufactured for Glaxo Pharmaceuticals, Research Triangle Park, NC 27709
by Roxane Laboratories, Inc., Columbus, OH 43216

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One Of A Kind

Please see Brief Summary of Prescribing Information on adjacent page.

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The Western Journal of Medicine

VOLUME 157 • NUMBER 6 DECEMBER 1992

BIOMEDICAL SCIENCE

631 Future Prospects for Treatment of Hemoglobinopathies
J A STAMATOYANNOPOULOS

ARTICLES

637 The Effect of Human Immunodeficiency Virus Infection on the Distribution and Outcome of Pneumonia in Intensive Care Units
K J TUCKER, B ANTON, and H J TUCKER

641 Submersion Injuries in Children Younger Than 5 Years in Urban Utah
L R JENSEN, S D WILLIAMS, D J THURMAN, and P A KELLER

645 Scombroid Fish Poisoning—Underreporting and Prevention Among Noncommercial Recreational Fishers
G A GELLERT, J RALLS, J HUSTON, and R MERRYMAN

Seizures After Eating a Snack Food Contaminated With the Pesticide Endrin—The Tale of the Toxic Taquitos
K WALLER, T J PRENDERGAST, A SLAGLE, and R J JACKSON

CONFERENCES AND REVIEWS

Orthostatic Hypotension—Causes, Evaluation, and Management
A S HOLLISTER

Eating Disorders—A Review and Update
E HALLER

EPITOMES

mportant Advances in Physical Medicine and Rehabilitation

ALERTS, NOTICES, AND CASE REPORTS

Pseudothrombocytopenia in a Child With the Acquired mmunodeficiency Syndrome
K WONG, R ROBERTSON, G NAGAOKA, E ONG, L PETZ, and E R STIEHM

Reflections on the Anion Gap in Hyperglycemia
VARON, M B JACOBS, and C A MAHONEY

arcinocythemia—A Terminal Manifestation of Metastatic reast Cancer
D M ABOULAFIA

RADIOLOGIC CASE

675 Thin-walled Lung Cavities and Cysts Due to AIDS-Related Pulmonary Infection
K PADMANABHAN and S VORA

COMMENTARY

677 Clinical Studies With Make-believe Drugs
J P LEWIS

EDITORIALS

679 Orthostatic Hypotension in Earthlings and Space Travelers • Has Our 'Healthy' Life-style Generated Eating Disorders?

CORRESPONDENCE

681 Whooping Cough in Infancy • Crohn's Disease—A Rare Disorder in American Indians • State AIDS Program Expansion • Cross-cultural Communication • A Friendship Bridge to Vietnam

LESSONS FROM THE PRACTICE

685 The Man Who Would Not Die
C G BAYNE

OTHER FEATURES

613 Subscription Information

618 In Memoriam

622 Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming

686 Poems

687 Volume Index

698 Classified Advertising

709 Instructions for Authors

710 Western State Medical Associations' Meetings

Detailed Table of Contents: 612, 614, 616

****
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- No clinically significant change in serum creatinine[1,2] or creatinine clearance[1,3]
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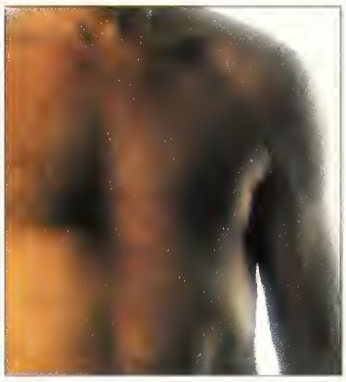

Maintains cardiac performance.

- No significant effect on heart rate*[7-10]
- No adverse effect on cardiac conduction[11,12] or contractility†[3,10,13-15]
- No alteration of digoxin clearance[16]

Does not compromise metabolic parameters.

- No clinically significant effect on serum glucose metabolism[17]
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- No known contraindications except for hypersensitivity to DynaCirc
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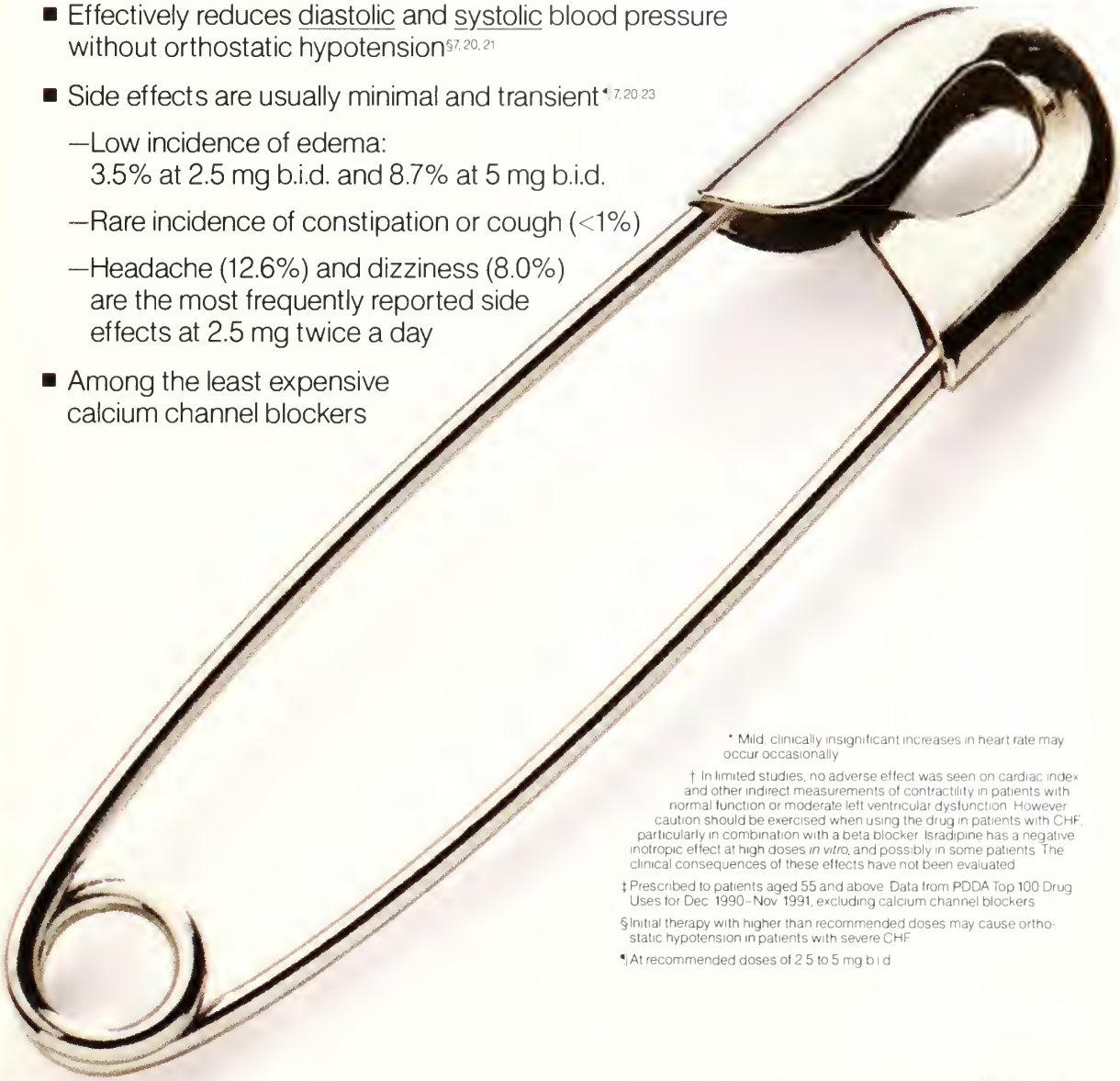

* Mild, clinically insignificant increases in heart rate may occur occasionally

† In limited studies, no adverse effect was seen on cardiac index and other indirect measurements of contractility in patients with normal function or moderate left ventricular dysfunction. However caution should be exercised when using the drug in patients with CHF, particularly in combination with a beta blocker. Isradipine has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. The clinical consequences of these effects have not been evaluated.

‡ Prescribed to patients aged 55 and above. Data from PDDA Top 100 Drug Uses for Dec. 1990–Nov. 1991, excluding calcium channel blockers.

§ Initial therapy with higher than recommended doses may cause orthostatic hypotension in patients with severe CHF.

¶ At recommended doses of 2.5 to 5 mg b.i.d.

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2.5 mg capsules (isradipine) 5 mg capsules

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Please see following page for brief summary of full Prescribing Information.

BRIEF SUMMARY
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DYNACIRC® (isradipine) CAPSULES

INDICATION

DynaCirc® (isradipine) is indicated in the management of hypertension. It may be used alone or concurrently with thiazide-type diuretics.

CONTRAINDICATIONS

DynaCirc® is contraindicated in individuals who have shown hypersensitivity to any of the ingredients in the formulation.

WARNINGS

None.

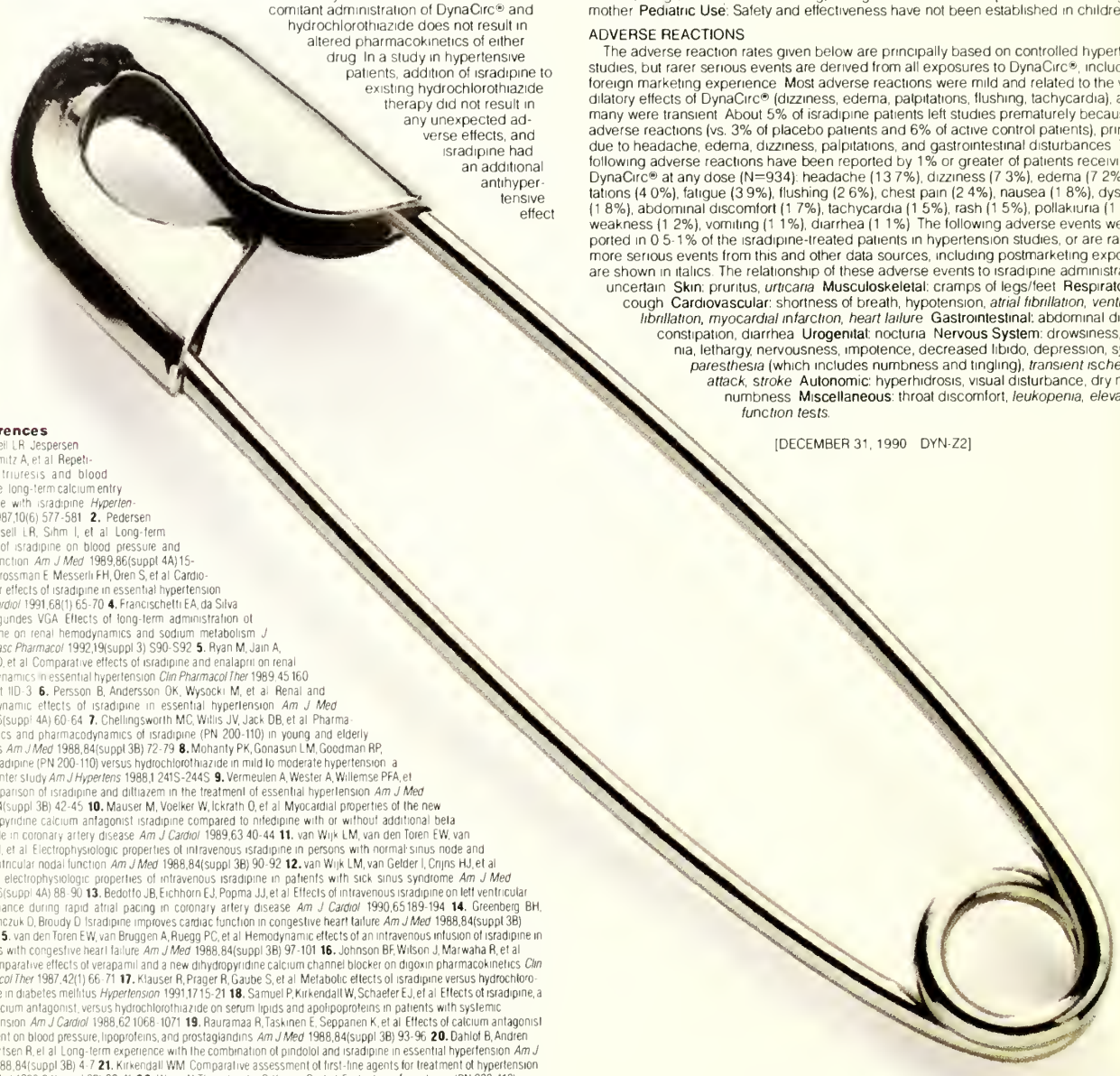
PRECAUTIONS

General: *Blood Pressure*: Because DynaCirc® decreases peripheral resistance, like other calcium blockers DynaCirc® may occasionally produce symptomatic hypotension. However, symptoms like syncope and severe dizziness have rarely been reported in hypertensive patients administered DynaCirc®, particularly at the initial recommended doses. *Use in Patients with Congestive Heart Failure*: Although acute hemodynamic studies in patients with congestive heart failure have shown that DynaCirc® reduced afterload without impairing myocardial contractility, it has a negative inotropic effect at high doses *in vitro*, and possibly in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker. **Drug Interactions**: *Nitroglycerin*: DynaCirc® has been safely coadministered with nitroglycerin. *Hydrochlorothiazide*: A study in normal healthy volunteers has shown that concomitant administration of DynaCirc® and hydrochlorothiazide does not result in altered pharmacokinetics of either drug. In a study in hypertensive patients, addition of isradipine to existing hydrochlorothiazide therapy did not result in any unexpected adverse effects, and isradipine had an additional antihypertensive effect. *Propranolol*: In a single dose study in normal volunteers coadministration of propranolol had a small effect on the rate but no effect on the extent of isradipine bioavailability. Coadministration of DynaCirc® resulted in significant increases in AUC (27%) and C_{max} (58%) and decreases in t_{max} (23%) of propranolol. *Digoxin*: The concomitant administration of DynaCirc® and digoxin in a single-dose pharmacokinetic study did not affect renal, nonrenal and total body clearance of digoxin. *Fentanyl Anesthesia*: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta blocker and a calcium channel blocker. Even though such interactions have not been seen in clinical studies with DynaCirc®, an increased volume of circulating fluids might be required if such an interaction were to occur. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Treatment of male rats for 2 years with 2.5, 12.5, or 62.5 mg/kg/day isradipine admixed with the diet resulted in dose dependent increases in the incidence of benign Leydig cell tumors and testicular hyperplasia relative to untreated control animals. A comparable endocrine effect was not evident in male patients receiving therapeutic doses of the drug on a chronic basis. Treatment of mice for two years with 2.5, 15, or 80 mg/kg/day isradipine in the diet showed no evidence of oncogenicity. There was no evidence of mutagenic potential based on the results of a battery of mutagenicity tests. No effect on fertility was observed in male and female rats. **Pregnancy**: *Pregnancy Category C*: There are no adequate and well controlled studies in pregnant women. DynaCirc® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers**: It is not known whether DynaCirc® is excreted in human milk. A decision should be made as to whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**: Safety and effectiveness have not been established in children.

ADVERSE REACTIONS

The adverse reaction rates given below are principally based on controlled hypertension studies, but rarer serious events are derived from all exposures to DynaCirc®, including foreign marketing experience. Most adverse reactions were mild and related to the vasodilatory effects of DynaCirc® (dizziness, edema, palpitations, flushing, tachycardia), and many were transient. About 5% of isradipine patients left studies prematurely because of adverse reactions (vs. 3% of placebo patients and 6% of active control patients), principally due to headache, edema, dizziness, palpitations, and gastrointestinal disturbances. The following adverse reactions have been reported by 1% or greater of patients receiving DynaCirc® at any dose (N=934): headache (13.7%), dizziness (7.3%), edema (7.2%), palpitations (4.0%), fatigue (3.9%), flushing (2.6%), chest pain (2.4%), nausea (1.8%), dyspnea (1.8%), abdominal discomfort (1.7%), tachycardia (1.5%), rash (1.5%), pollakiuria (1.5%), weakness (1.2%), vomiting (1.1%), diarrhea (1.1%). The following adverse events were reported in 0.5-1% of the isradipine-treated patients in hypertension studies, or are rare, but more serious events from this and other data sources, including postmarketing exposure, are shown in italics. The relationship of these adverse events to isradipine administration is uncertain. **Skin**: pruritus, *urticaria*. **Musculoskeletal**: cramps of legs/feet. **Respiratory**: cough. **Cardiovascular**: shortness of breath, hypotension, *atrial fibrillation, ventricular fibrillation, myocardial infarction, heart failure*. **Gastrointestinal**: abdominal discomfort, constipation, diarrhea. **Urogenital**: nocturia. **Nervous System**: drowsiness, insomnia, lethargy, nervousness, impotence, decreased libido, depression, *syncope, paresthesia* (which includes numbness and tingling), *transient ischemic attack, stroke*. **Autonomic**: hyperhidrosis, visual disturbance, dry mouth, numbness. **Miscellaneous**: throat discomfort, *leukopenia, elevated liver function tests*.

[DECEMBER 31, 1990 DYN-Z2]



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(Jensen LR, Williams SD, Thurman DJ, Keller PA: Submersion injuries in children younger than 5 years in urban Utah. West J Med 1992 Dec; 157:641-644)

Submersion injuries of children younger than 5 years in 4 urban Utah counties from 1984 through 1988 were studied retrospectively to identify associated risk factors. Infants younger than 1 year had the highest rates of both submersion injuries and deaths. The incidence of bathtub drownings was 2 to 3 times higher than reported national rates. All bathtub drownings occurred while the victim was bathing with a young sibling (10 months to 7 years of age) without adult supervision. All drownings in pools and moving bodies of water (rivers, irrigation ditches) resulted from unintentional falls into the water rather than from swimming and wading activities. Drowning prevention strategies should focus on educating parents about the risk of young children bathing with siblings in the absence of adult supervision and fencing regulations for pools and open bodies of moving water.

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NEAR-DROWNING
BATHTUB DROWNING

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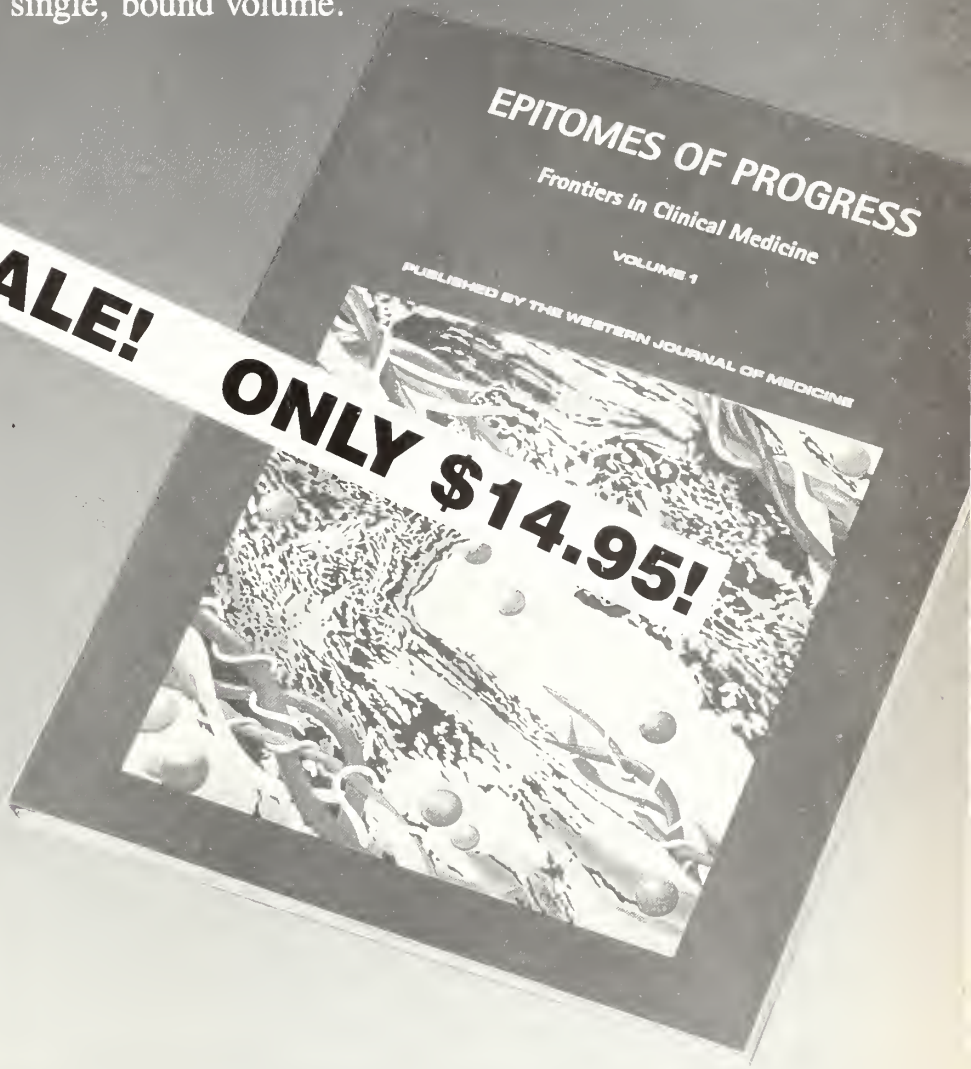

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CONTENTS

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631 **Future Prospects for Treatment of Hemoglobinopathies**

JOHN A. STAMATOYANNOPOULOS

From the University of Washington School of Medicine, Seattle. This paper was chosen as the winner of The Western Journal of Medicine's *1992 Medical Student Writing Competition.*

ARTICLES

637 **The Effect of Human Immunodeficiency Virus Infection on the Distribution and Outcome of Pneumonia in Intensive Care Units**

KELLY J. TUCKER, MD; BETTE ANTON, MLS; and HARVEY J. TUCKER, MD

From the Intensive Care Unit, California Pacific Medical Center, San Francisco, and the Health Sciences Information Service, University of California, Berkeley.

641 **Submersion Injuries in Children Younger Than 5 Years in Urban Utah**

LLOYD R. JENSEN, MD; SCOTT D. WILLIAMS, MD, MPH; DAVID J. THURMAN, MD, MPH; and PATRICIA A. KELLER, RN

From the Department of Pediatrics, University of Utah School of Medicine, and the Divisions of Community Health Services and Family Health Services, State of Utah Department of Health, Salt Lake City.

645 **Scombroid Fish Poisoning—Underreporting and Prevention Among Noncommercial Recreational Fishers**

GEORGE A. GELLERT, MD, MPH, MPA; JOHN RALLS, REHS; CORWIN BROWN, MS, REHS; JAMES HUSTON, MS, REHS; and ROBERT MERRYMAN, MPH, REHS

From the Orange County Health Care Agency, Santa Ana, California.

648 **Seizures After Eating a Snack Food Contaminated With the Pesticide Endrin—The Tale of the Toxic Taquitos**

KIRSTEN WALLER, MD, MPH; THOMAS J. PRENDERGAST, MD, MPH; ALAN SLAGLE, PharmD; and RICHARD J. JACKSON, MD, MPH

From the Division of Field Epidemiology, Centers for Disease Control, Atlanta, Georgia; the County of Orange Health Care Agency, Santa Ana; the California Department of Health Services, Sacramento; and the California Environmental Protection Agency, Berkeley. Dr Waller is currently with the Environmental Health Investigation Branch, California Department of Health Services, Berkeley, and Dr Prendergast is currently with the Department of Public Health, County of San Bernardino, San Bernardino, California.

CONFERENCES AND REVIEWS

652 **Orthostatic Hypotension—Causes, Evaluation, and Management**

ALAN S. HOLLISTER, MD, PhD

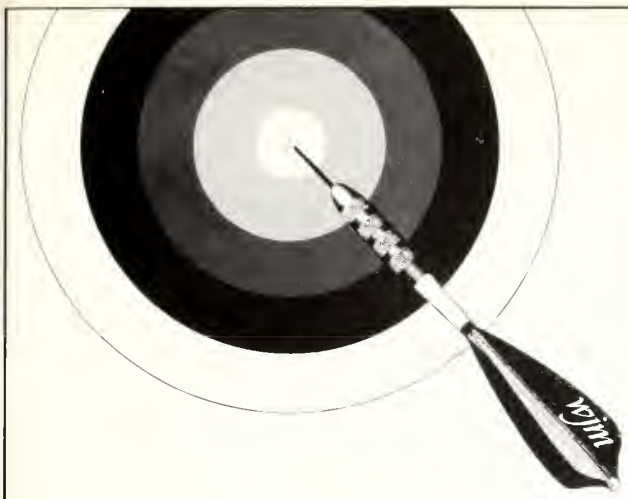
From the Division of Clinical Pharmacology, University of Colorado Health Sciences Center, Denver.

658 **Eating Disorders—A Review and Update**

ELLEN HALLER, MD

From the Langley Porter Psychiatric Institute, University of California, San Francisco, School of Medicine.

(Continued on Page 614)



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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(Continued from Page 612)

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Physical Medicine and Rehabilitation

Items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

663 **Late Effects of Poliomyelitis—An Update on Fatigue and Weakness**
STANLEY K. YARNELL, MD

663 **Prophylaxis and Treatment of Posttraumatic Epilepsy With Phenytoin**
TERESA L. MASSAGLI, MD

664 **Neurobehavioral and Family Functioning Following Traumatic Brain Injury in Children**
CRAIG M. McDONALD, MD, and KENNETH M. JAFFE, MD

665 **Treatment of Postconcussion Syndrome**
JAY M. UDMOTD, PhD; PETER C. ESSELMAN, MD; and DIANA D. CARDENAS, MD

665 **Family Support and Stroke Rehabilitation**
JEFFREY TERADKA, MD, and RENEE BURGARD, LCSW

666 **Focal Dystonia in Musicians**
SCOTT E. BROWN, MD

666 **Venous Thromboembolism in Stroke**
MURRAY E. BRANDSTATER, MD, PhD

ALERTS, NOTICES, AND CASE REPORTS

668 **Pseudothrombocytopenia in a Child With the Acquired Immunodeficiency Syndrome**
VICTOR K. WONG, MD; RICHARD ROBERTSON, MT; GAIL NAGAOKA, MT; EDDIE ONG, MT; LAWRENCE PETZ, MD; and E. RICHARD STIEHM, MD
From the Department of Pediatrics, Southern California Permanente Medical Group, Bellflower, California, and the Departments of Pathology and Laboratory Medicine and of Pediatrics, University of California, Los Angeles, School of Medicine.

670 **Reflections on the Anion Gap in Hyperglycemia**
JOSEPH VARON, MD; MICHAEL B. JACOBS, MD; and CYNTHIA A. MAHONEY, MD
From the Department of Medicine, Nephrology Division, Stanford University Medical Center, Stanford, California. Dr Voron is now with the Pulmonary and Critical Care Medicine Section, Baylor College of Medicine, Houston, Texas.

672 **Carcinocythemia—A Terminal Manifestation of Metastatic Breast Cancer**
DAVID M. ABDULAFIA, MD
From the Division of Hematology and Oncology, Virginia Mason Medical Center, and the Division of Hematology, University of Washington School of Medicine, Seattle.

RADIOLOGIC CASE

675 **Thin-walled Lung Cavities and Cysts Due to AIDS-Related Pulmonary Infection**
KRISHNAN PADMANABHAN, MD, and SHARAD VORA, MD
From the Pulmonary Disease Department, Coney Island Hospital, Brooklyn, New York, and the State University of New York Health Science Center at Brooklyn.

COMMENTARY

677 **Clinical Studies With Make-believe Drugs**
JERRY P. LEWIS, MD
From the Division of Hematology and Oncology, University of California, Davis, School of Medicine.

(Continued on Page 616)

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(Continued from Page 614)

EDITORIALS

679 **Orthostatic Hypotension in Earthlings and Space Travelers**
DAVID ROBERTSON, MD; F. ANDREW GAFFNEY; and ITALO BIAGGIONI
From the Center for Space Physiology and Medicine, Vanderbilt University, Nashville, Tennessee.

679 **Has Our 'Healthy' Life-style Generated Eating Disorders?**
JOEL YAGER, MD
From the Neuropsychiatric Institute and Hospital, Center for the Health Sciences, University of California, Los Angeles.

CORRESPONDENCE

681 **Whooping Cough in Infancy**
WAIN ALLEN, MD, and CYNTHIA CAMPBELL BARNES, FNP

682 **Crohn's Disease—A Rare Disorder in American Indians**
SUSAN M. CONGILOSI, MD; DOUGLAS E. ROSENDALE, DO; and DORIS L. HERMAN, MD

683 **State AIDS Drug Program Expansion**
WAYNE E. SAUSEDA

683 **Cross-cultural Communication**
MARVIN L. AUERBACK, MD

683 **A Friendship Bridge to Vietnam**
THEODORE C. NING, Jr, MD

LESSONS FROM THE PRACTICE

685 **The Man Who Would Not Die**
C. GRESHAM BAYNE, MD
Dr Bayne is in private practice in San Diego, California.

OTHER FEATURES

613 **Subscription Information**

618 **In Memoriam**

622 **Continuing Medical Education Activities in California, Hawaii, and Nevada; Colorado; Idaho; New Mexico; Utah; Washington; Wyoming**

686 **Poems**

687 **Volume Index**

698 **Classified Advertising**

709 **Instructions for Authors**

710 **Western State Medical Associations' Meetings**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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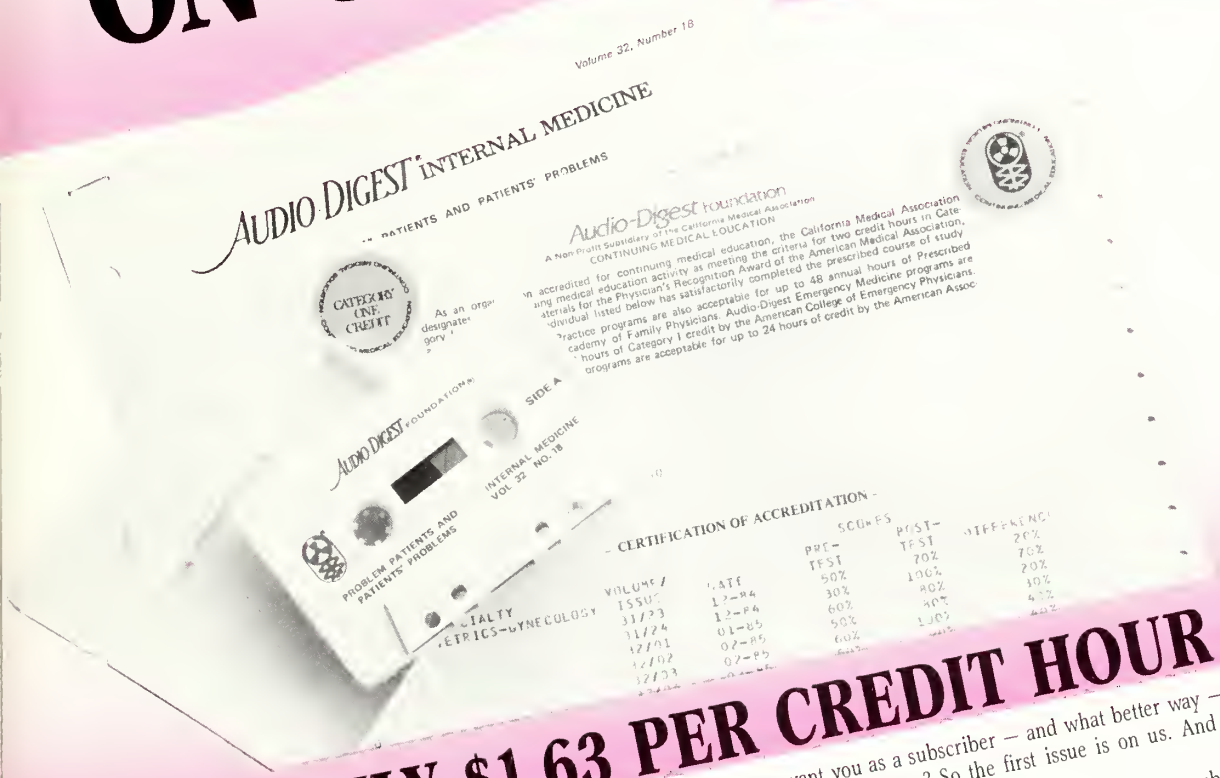

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In Memoriam

California Medical Association

Boscoe, Anthony R., Sacramento. Died Oct 12, 1992, aged 91. Graduate of Stanford University School of Medicine, Stanford, California, 1933. Licensed in California in 1933. Dr Boscoe was a member of the Sacramento-El Dorado Medical Society.

Canfield, Merritt C., San Diego. Died Sep 27, 1992, aged 88. Graduate of Northwestern University Medical School, Chicago, Illinois, 1931. Licensed in California in 1931. Dr Canfield was a member of the San Diego County Medical Society.

Collins, John Austin, Stanford. Died Sep 1992, aged 58. Graduate of Columbia University, New York, 1958. Licensed in California in 1977. Dr Collins was a member of the Santa Clara County Medical Association.

Cronin, Daniel J., San Francisco. Died Oct 21, 1992, aged 80. Graduate of Creighton University, Omaha, Nebraska, 1936. Licensed in California in 1936. Dr Cronin was a member of the San Francisco Medical Society.

Curtis, Robert H., San Francisco. Died Oct 3, 1992, aged 70. Graduate of Cornell University, New York, 1951. Licensed in California in 1951. Dr Curtis was a member of the San Francisco Medical Society.

Delavega, Frederick J., San Diego. Died Jul 8, 1992, aged 70. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1946. Licensed in California in 1952. Dr Delavega was a member of the San Diego County Medical Society.

Dillon, Victor M., San Francisco. Died Oct 18, 1992, aged 92. Graduate of St Louis University, St Louis, Missouri, 1928. Licensed in California in 1928. Dr Dillon was a member of the San Francisco Medical Society.

Dinwiddie, Robert C., Redlands. Died Sep 17, 1992, aged 38. Graduate of University of California, Los Angeles, School of Medicine, 1979. Licensed in California in 1980. Dr Dinwiddie was a member of the San Bernardino County Medical Society.

Ekegren, James K., San Luis Obispo. Died Oct 6, 1992, aged 62. Graduate of University of California, Los Angeles, 1956. Dr Ekegren was a member of the San Luis Obispo County Medical Society.

Fischer, Golda, Berkeley. Died Aug 6, 1992, aged 79. Graduate of Medical College of South Carolina, Charleston, 1943. Licensed in California in 1945. Dr Golda was a member of the Alameda-Contra Costa Medical Association.

Gallaher, John A., Walnut Creek. Died Jun 20, 1992, aged 78. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1940. Licensed in California in 1944. Dr Gallaher was a member of the Alameda-Contra Costa Medical Association.

Gardiner, Theodore D., Livermore. Died May 29, 1992, aged 63. Graduate of University of Maryland School of Medicine, Baltimore, 1959. Licensed in California in 1960. Dr Gardiner was a member of the Alameda-Contra Costa Medical Association.

Gibbings, Raymond J., San Diego. Died Aug 12, 1992, aged 62. Graduate of George Washington University School of Medicine, Washington, DC, 1956. Licensed in California in 1959. Dr Gibbings was a member of the San Diego County Medical Society.

Grief, Marvin H., San Jose. Died Sep 28, 1992, aged 64. Graduate of University of Washington School of Medicine, Seattle, 1954. Licensed in California in 1957. Dr Grief was a member of the Santa Clara County Medical Association.

Katz, Hyman M., Oakland. Died Aug 8, 1992, aged 85. Graduate of University of California, Irvine, California College of Medicine, 1962. Licensed in California in 1975. Dr Katz was a member of the Alameda-Contra Costa Medical Association.

Lammel, Harry G., Vallejo. Died Oct 26, 1992, aged 78. Graduate of University of Nebraska, Omaha, 1942. Dr Lammel was a member of the Solano County Medical Society.

Madison, Mitchell, Palo Alto. Died Sep 9, 1992, aged 71. Graduate of University of Rochester School of Medicine, Rochester, New York. Licensed in California in 1954. Dr Madison was a member of the Santa Clara County Medical Association.

Mitchell, James E., San Ramon. Died Sep 21, 1992, aged 48. Graduate of Vanderbilt University School of Medicine, Nashville, Tennessee, 1969. Licensed in California in 1970. Dr Mitchell was a member of the Alameda-Contra Costa Medical Association.

Morrison, Norman D., Jr, San Mateo. Died Aug 27, 1992, aged 84. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, 1934. Licensed in California in 1935. Dr Morrison was a member of the San Mateo County Medical Society.

O'Donnell, Bernard Vincent, Vallejo. Died Sep 12, 1992, aged 76. Graduate of Georgetown University School of Medicine, Washington, DC, 1943. Licensed in California in 1946. Dr O'Donnell was a member of the Solano County Medical Society.

Philips, Irving, San Francisco. Died Aug 29, 1992, aged 70. Graduate of University of Illinois College of Medicine, Chicago, 1948. Licensed in California in 1955. Dr Philips was a member of the San Francisco Medical Society.

Rosenberg, Benjamin B., Eureka. Died Aug 12, 1992, aged 71. Graduate of University of California, San Francisco, School of Medicine, 1944. Licensed in California in 1945. Dr Rosenberg was a member of the Humboldt-Del Norte Medical Society.

Rush, Norman J., Concord. Died Feb 16, 1992, aged 79. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1939. Licensed in California in 1947. Dr Rush was a member of the Alameda-Contra Costa Medical Association.

Sibul, Ebba Kuldvere, Oakland. Died May 21, 1992, aged 72. Graduate of University of Heidelberg, Germany, 1948. Licensed in California in 1952. Dr Sibul was a member of the Alameda-Contra Costa Medical Association.

Smith, Lowell R., San Diego. Died Aug 27, 1992, aged 70. Graduate of University of Iowa College of Medicine, Iowa City, 1946. Licensed in California in 1954. Dr Smith was a member of the San Diego County Medical Society.

Smitter, Robert C., Covina. Died Oct 26, 1992, aged 73. Graduate of Northwestern University, Chicago, Illinois, 1945. Licensed in California in 1951. Dr Smitter was a member of the Los Angeles County Medical Association.

Spratt, Robert J., Napa. Died Sep 27, 1992, aged 74. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1942. Licensed in California in 1961. Dr Spratt was a member of the Napa County Medical Society.

Steiss, Charles F., San Francisco. Died Apr 27, 1992, aged 85. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1931. Licensed in California in 1932. Dr Steiss was a member of the San Francisco Medical Society.

Swartout, Roy III, Temple City. Died Aug 2, 1992, aged 70. Graduate of State University of New York at Buffalo Medical School, 1945. Licensed in California in 1948. Dr Swartout was a member of the San Diego County Medical Society.

Thompson, William H., Burlingame. Died Aug 9, 1992, aged 77. Graduate of University of Chicago College of Medicine, Chicago, Illinois, 1942. Licensed in California in 1950. Dr Thompson was a member of the San Mateo County Medical Society.

(Continued on Page 619)

In Memoriam

(Continued from Page 618)

VASKO, JOHN R., Oakland. Died Sep 1, 1992, aged 91. Graduate of Long Island Medical College, New York, 1925. Licensed in California in 1926. Dr Vasko was a member of the Alameda-Contra Costa Medical Association.

❧

WAPNICK, ANTHONY A., San Diego. Died Sep 14, 1992, aged 50. Graduate of University of Witwatersrand, Johannesburg, South Africa, 1965. Licensed in California in 1979. Dr Wapnick was a member of the San Diego County Medical Society.

❧

WILLIAMS, JAMES A., Sacramento. Died Jul 21, 1992, aged 69. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1947. Licensed in California in 1947. Dr Williams was a member of the Sacramento-El Dorado Medical Society.

Idaho Medical Association

LESSER, LOUIS F., Boise. Died Oct 21, 1992, aged 88. Graduate of University of Colorado, Denver, 1934. Licensed in Idaho in 1935. Dr Lesser was a member of the Ada County Medical Society.

New Mexico Medical Society

ALBRECHT, PHILIP, Espanola. Died Sep 4, 1992, aged 46. Graduate of University of Illinois College of Medicine, Chicago, 1970. Licensed in Arizona in 1974. Dr Albrecht was a member of the Rio Arriba County Medical Society.

❧

KEMPERS, BERT, Albuquerque. Died Oct 24, 1992, aged 90. Graduate of Northwestern University, Chicago, Illinois, 1929. Licensed in Arizona in 1938. Dr Kempers was a member of the Greater Albuquerque Medical Society.

❧

KOSICKI, ZIGMUND W., Santa Fe. Died Sep 13, 1992, aged 72. Graduate of Stritch School of Medicine, Maywood, Illinois, 1951. Licensed in California in 1964. Dr Kosicki was a member of the Santa Fe County Medical Society.

❧

WILKINSON, LAWRENCE, Albuquerque. Died Aug 9, 1992, aged 76. Graduate of Baylor College of Medicine, Houston, Texas, 1942. Licensed in New Mexico in 1949. Dr Wilkinson was a member of the Greater Albuquerque Medical Society.

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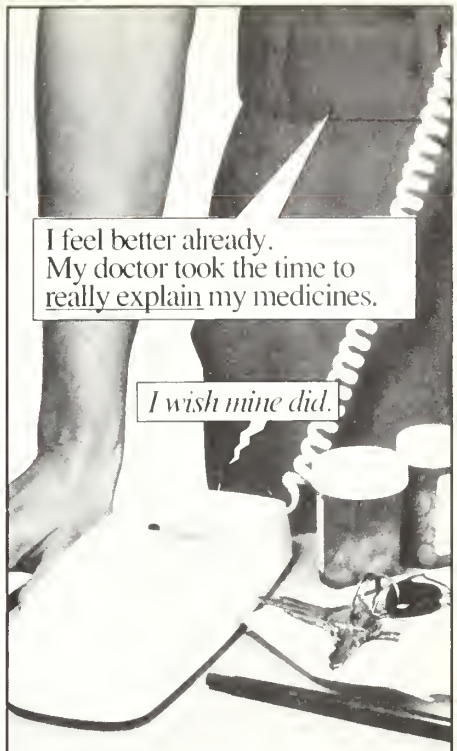

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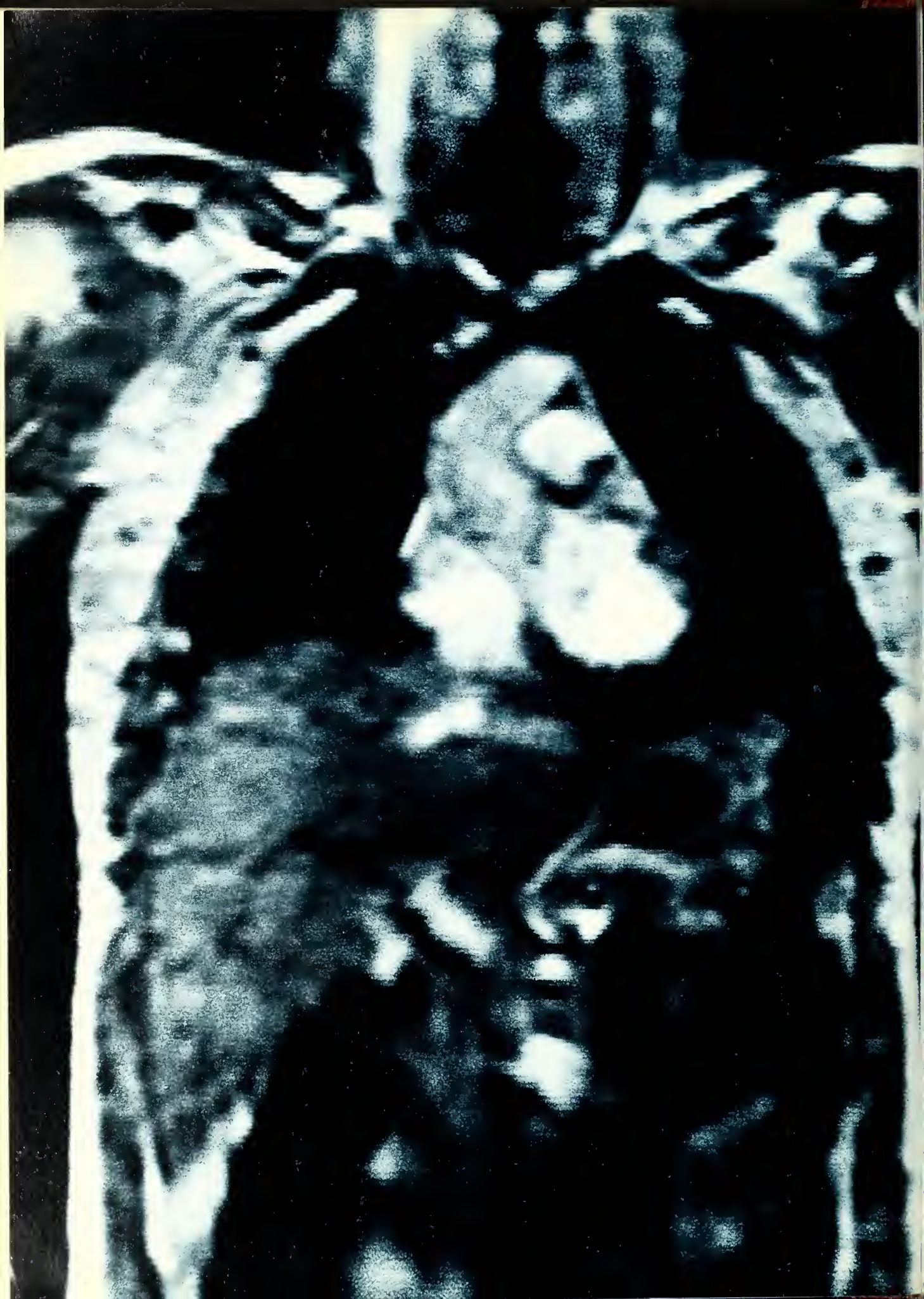

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ALLERGY/IMMUNOLOGY

May 7-8—**Asthma and Allergy in the 1990s.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 10 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

ANESTHESIOLOGY

January 6-9—**Anesthesia Update.** UCSD at Hotel del Coronado, San Diego. Wed-Sat. Contact: UCSD.

January 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach, Maui, Hawaii. 1 wk. 21 hrs. $395. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

January 29-31—**31st Clinical Conference in Pediatric Anesthesiology.** Children's Hospitals Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 19-23—**67th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Diego Marriott Hotel & Marina, San Diego. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131-2553. (216) 642-1124.

March 26-28—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort, Dana Point. Fri-Sun. 9 hrs. $175-$245. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

CARDIOLOGY

January 21-23—**Cardiology '93.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, Conference Manager, PO Box 2586, La Jolla 92038. (619) 459-1564.

January 21-23—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. 22 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

January 22-23—**Arrhythmias: Interpretation, Diagnosis and Management.** American College of Emergency Physicians at Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

February 19-20—**Arrhythmias: Interpretation, Diagnosis and Management.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 11-13—**3rd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 26-27—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 26-28—**Thromboembolic and Primary Vascular Disease: Diagnosis and Management.** UCSD at Sheraton Harbor Island. Fri-Sun. Contact: UCSD.

April 2-3—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Le Meridien Hotel, San Diego. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 23-24—**Coronary Heart Disease Update.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

DERMATOLOGY

January 15-17—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. Contact: UCSD.

January 22-24—**Cutaneous Malignancies: 1993 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. $350. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

January 13—**Trauma Coordinator Symposium.** UCSD at Hotel del Coronado, San Diego. Wed. 8 hrs. $100. Contact: UCSD.

January 14-17—**The California Trauma Conference.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 20 hrs. $400. Contact: UCSD.

January 18-22—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

January 23-30—**Wound Management.** UCSD at Royal Waikoloan, Kohala Coast, Island of Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Royal Lahaina Resort, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 21-26—**Emergency Medicine: 1993.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

March 15-19—**Emergency Medicine Symposia II.** UCSD at La Jolla. Mon-Fri. Contact: UCSD.

March 31-April 3—**Advances in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Wed-Sat. 19 hrs. Contact: UCSF.

May 12-16—**Wound Management Workshop for Primary Care Physicians.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $475. Contact: UCSD.

ENDOCRINOLOGY/METABOLISM

February 19-20—**New Horizons in Diabetes Therapy.** Scripps Clinic and Research Foundation at Scripps Memorial Hospital, La Jolla. Fri-Sat. $175. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5—**19th Annual Diabetes Symposium.** UCD at Sheraton Sunrise, Rancho Cordova. Fri. 6 hrs. Contact: UCD.

March 10-11—**Advances in Endocrinology and Metabolism.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 12-13—**Diabetes Update.** UCSF at Ritz-Carlton Hotel, San Francisco. Fri-Sat. 11 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 12-14—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 12-15—**45th Annual Scientific Assembly.** California Academy of Family Physicians at Wyndham Hotel and Palm Springs Convention Center. Fri-Mon. 25.5 hrs. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

(Continued on Page 624)

American College of Physicians

Annual Session

APRIL 1 - 4

Pre-Session Courses

MARCH 30 - 31

1993 Meeting Theme:
Prevention: Medicine's New Frontier

PRE-REGISTRATION DEADLINE: FEBRUARY 19, 1993

Experience the full educational value of Annual Session, April 1-4, 1993, with 1- and 2-day Pre-Session courses, on March 30-31. Maximize your learning while you earn CME credits at internal medicine's most highly respected yearly meeting.

10% Pre-Session/ Annual Session Discount
Sign-up for Pre-Session and Annual Session and save 10% off the combined fees!

How to Register

ACP Membership: See your Advance Program mailed in December for meeting information and complete registration materials.

Nonmembers: Watch for a schedule of events and a registration form in the Annual Session Digest appearing in the December 15, 1992, and January 1 and February 1, 1993, issues of *Annals of Internal Medicine.*

Register Now! Avoid on-site delays and additional fees.

Information Hotline: 800-523-1546, ext. 2429

(Continued from Page 622)

February 20—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium. Sat. 6 hrs. Contact: UCD.

March 24-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Fri. 15.5 hrs. $300. Contact: UCSF, Department of Family and Community Medicine.

April 10-17—**Primary Care Medicine: Update 1993.** UCSF at Maui Inter-Continental Hotel, Wailea, Hawaii. 1 week. 20 hrs. $545. Contact: UCSF.

April 22-24—**Rheumatology for Primary Care Physicians.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 14 hrs. Contact: UCSF.

April 22-25—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GERIATRICS

January 19-22—**Intensive Course in Geriatric Medicine.** UCLA at Ritz-Carlton Hotel, Marina del Rey. Tues-Fri. 29 hrs. $625. Contact: UCLA.

February 4-5—**Alzheimer's Disease New Advances in Treatment.** UCSD at San Diego. Fri-Sat. Contact: UCSD.

HEMATOLOGY

February 14-17—**Clinical Hematology and Oncology: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sun-Wed. 18 hrs. $385. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 11-13—**Recent Advances in Autologous Hematopoietic Stem Cell Transplantation.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sat. 16 hrs. $300. Contact: UCSD.

March 17-20—**5th International Symposium on Blood Substitutes.** UCSD at Sheraton Harbor Island. Wed-Sat. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

INFECTIOUS DISEASES

January 5-7—**Part-time Intensive Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

January 12-23—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1½ weeks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

February 1-5—**Advanced—STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Fri. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

February 5-6—**11th Annual Practical Update of Infectious Diseases.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. 12 hrs. $160. Contact: UCD.

March 16-18—**Planning and Evaluation HIV Programs.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 23-25—**STD/HIV for Outreach Workers.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 30-31—**HIV Update.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Wed. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 12-24—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1¾ wks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 28-30—**Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. Contact: UCSF.

May 24-29—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Sat. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

INTERNAL MEDICINE

January 28-30—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Sat-Mon. Contact: UCSD.

February 5-7—**State of the Art Urology.** UCLA at Ritz-Carlton, Marina del Rey. Fri-Sun. Contact: UCLA Extension.

February 6—**California Association of Cytology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

February 20-25—**Topics and Advances in Internal Medicine.** UCSD at Hyatt Regency. Sun-Thurs. 45 hrs. $595. Contact: UCSD.

February 26-27—**Advances in Vascular Diseases.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 19-25—**Internal Medicine 1993: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Tues. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5-8—**Controversies and Agreements in Internal Medicine.** Group Health Cooperative at Intercontinental Hotel, Maui, Hawaii. Mon-Thurs. 19 hrs. $425. Contact: GHC, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

NEUROLOGY

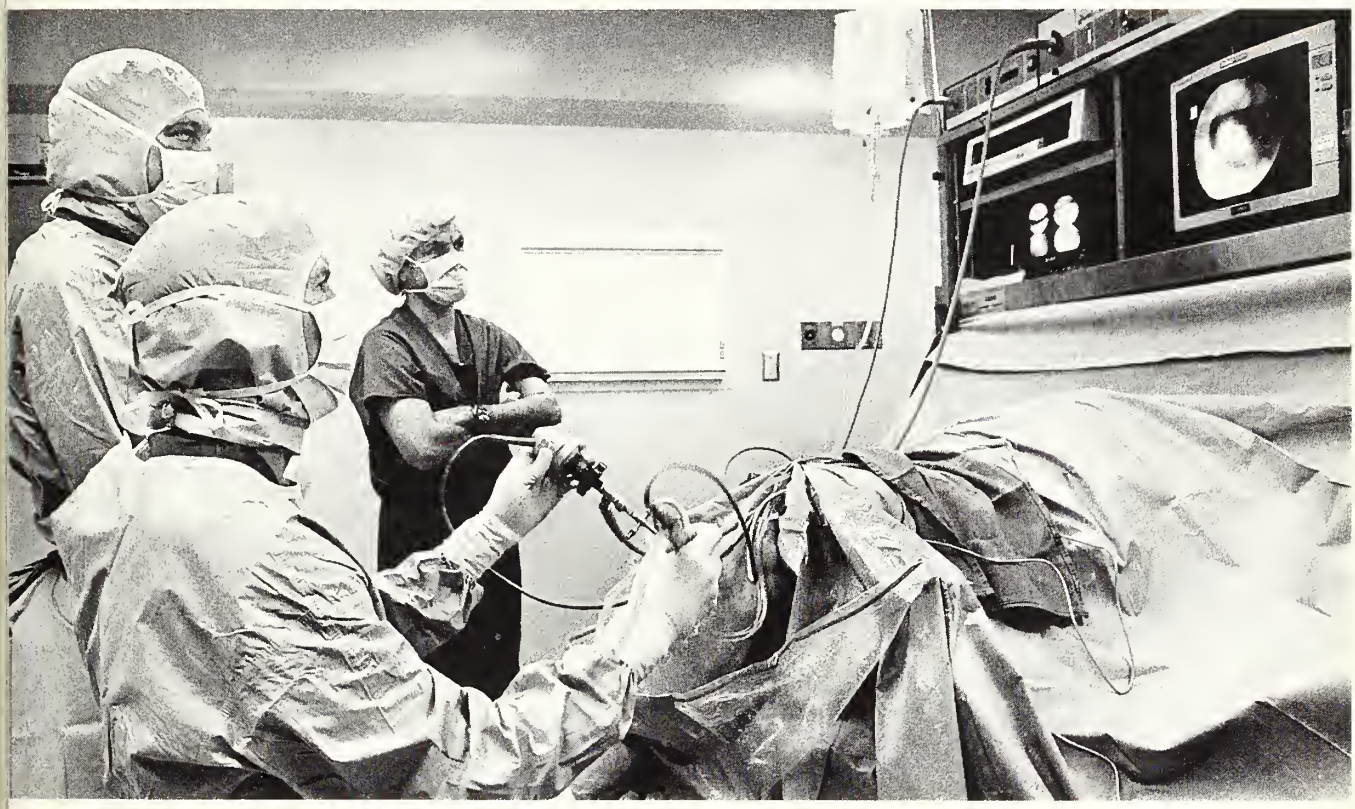
February 4-6—**16th Annual: Neurology for Non-Neurologists.** UCSD at Doubletree Hotel Horton Plaza, San Deigo. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 11-13—**26th Annual Recent Advances in Neurology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 15 hrs. $345. Contact: UCSF.

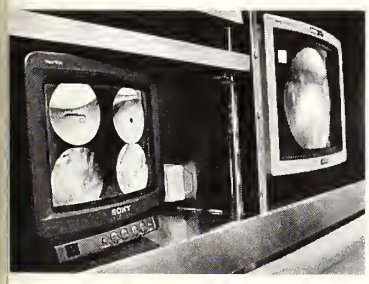
May 14-16—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sun. 12 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

(Continued on Page 626)

LET ME TELL YOU ABOUT THE FIRST TIME I WAS ON TELEVISION.



As a family practice physician, Dr. Alvin Sockolov had assisted in operating room number 7 at Sutter General Hospital many times. But after re-injuring his knee, there he was, undergoing ACL surgery at the hands of Dr. David Coward. While choosing surgery was a difficult decision, choosing Sutter General was not. "Dr. Coward prefers to operate at Sutter General," says Dr. Sockolov. "A surgeon needs special equipment, fine instruments, and a capable staff to feel comfortable. Sutter General has what physicians need for procedures to run smoothly." More orthopedic surgeries are performed at Sutter General Hospital than at any other hospital in the region. Advanced diagnostic equipment, specially trained orthopedic nurses, and a team of rehabilitation specialists all help give Sutter General a reputation that's unmatched in Northern California. In addition, educational programs, a health library, outpatient and extended care facilities provide both physicians and patients with the best resources available. "The only problem I had with Sutter General," says Dr. Sockolov, "was that when it came time to leave, I didn't want to go. Everything was top-notch." For more information about available services, call Sutter Orthopedic Center at Sutter General Hospital in Sacramento, (916) 733-8880.



Alvin Sockolov, M.D.

Sutter Orthopedic Center
SUTTER GENERAL HOSPITAL

(Continued from Page 624)

OB/GYN

January 17-19—**Annual Ambulatory Gynecology Update: 1993.** UCD at Incline Village, Nevada. Sun-Tues. 14 hrs. $260. Contact: UCD.

February 11-14—**48th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: C. James Dowden, OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 17-19—**Contemporary Obstetrical and Transvaginal Ultrasound.** UCSD. Wed-Fri. Contact: UCSD.

March 13—**Women's Health Issues.** UCD at Cancer Center Auditorium. Sat. Contact: UCD.

March 18-20—**Prevention of Prematurity and Neonatal Mortality.** UCSD at Loew's Coronado. Thurs-Sat. 13 hrs. $370. Contact: UCSD.

April 14-18—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Susan Butler, PCFS, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 25-February 5—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. 1½ weeks. 80 hrs. $1400. Contact: UCSF.

February 8-12—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

March 4-5—**Dimensions of Caring 1993: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Doubletree Hotel Horton Plaza, La Jolla. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-9592.

OPHTHALMOLOGY

January 30—**Genetic Disease and the Eye.** Cedars Sinai Medical Center Division of Ophthalmology at Ma Maison Hotel, Los Angeles. Sat. 8 hrs. $50. Contact: Yaron Rabinowitz, MD, 444 S San Vicente Blvd, Ste 600, Los Angeles 90048. (310) 855-2613.

May 14-15—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OTOLARYNGOLOGY

December 1992-April 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Sun-Fri. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

February 19-21—**Midwinter Clinical Conference for Otolaryngologists and Ophthalmologists.** Research Study Club of Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Fri-Sun. 15 hrs. Contact: Research Study Club, PO Box 1216, Murrieta 92564. (714) 677-4482.

PATHOLOGY

January 25-29—**American Society of Clinical Pathologists Workshop Week in Medical Technology.** ASCP at Airport Hilton, San Francisco. Mon-Fri. 7 hrs. Contact: ASCP, (800) 621-4142.

March 13—**Update on Dialysis Access: Creation, Maintenance and Salvage.** UCSD at Le Meridien. Sat. Contact: UCSD.

March 19-20—**Pathology Forum: 1993.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 17—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-6310.

PEDIATRICS

January 26-30—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Hyatt Regency, La Jolla. Tues-Sat. 28 hrs. Contact: Center for Child Protection, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4950.

February 15-17—**Pediatrics Update.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

February 26-28—**Current Concepts in Pediatric Medicine: 1993.** Children's Hospital San Diego and American Academy of Pediatrics at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Continuing Education, 8001 Frost St, San Diego 92123. (619) 576-4072.

April 2-3—**Ambulatory Pediatrics: Special Spotlight Morning in Neonatology.** UCD at Sacramento Inn. Fri-Sat. 10 hrs. Contact: UCD.

April 3-10—**Pediatrics Emergencies.** UCSD at Poipu Beach Hotel and Waiohai Resort, Kauai, Hawaii. 1 wk. 21 hrs. $450. Contact: UCSD.

PSYCHIATRY

January 24-29—**19th Annual Midwinter Program for Psychiatrists: Special Focus on Hysteria.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 12-14—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Catamaran Hotel, San Diego. Fri-Sun. Contact: UCSD.

February 27—**Sleep Apnea: New Insights into Pathophysiology and Treatment.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 4-6—**51st Annual Meeting of the American Psychosomatic Society.** UCSD at Omni Hotel, San Diego. Thurs-Sat. Contact: UCSD.

RADIOLOGY

December 28-January 2—**Year End Review of Imaging and Intervention.** UCSD at Intercontinental Hotel, Wailea, Maui, Hawaii. Mon-Sat. 25 hrs. $550-$595. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 13-15—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Wed-Fri. 15 hrs. $500. Contact: UCSD.

January 15-17—**45th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.75 hrs. $125-$450. Contact: LARS, MWRC, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078.

January 16-17—**Interventional Radiology Update.** Stanford University at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 7.5 hrs. $200-$250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 18-20—**Neuroradiology Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 17.5 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 21-24—**Breast Imaging Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 17.25 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 15-19—**Diagnostic Imaging Update: Mammography, MRI, Body Imaging, Neuroradiology, Pediatrics.** Stanford University Medical Center at Ritz-Carlton, Palm Beach. Mon-Fri. 23.75 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 22-26—**Diagnostic Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Kapalua Bay, Maui, Hawaii. Mon-Fri. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-27—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Wed-Sat. 15 hrs. $500. Contact: UCSD.

March 8-12—**8th Annual San Diego Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 29 hrs. $595. Contact: Dawne Ryals, PO Box 1925, Roswell 30077-1925. (404) 641-9773.

March 10-12—**13th Annual Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: Crest Organization (415) 595-2704.

March 13—**Focus on Hemodialysis Access: Creation, Maintenance and Salvage.** American College of Emergency Physicians at Le Meridien, San Diego (Coronado). Sat. 6.5 hrs. $75. Contact: UCSD.

March 15-17—**Squaw Valley Minimally Invasive Conference for Diagnostic Radiologists and Surgeons.** UCD at Resort at Squaw Creek, Squaw Valley. Mon-Wed. Contact: UCD.

March 28-April 2—**General Radiology Review Course.** UCLA at Doubletree Hotel, Marina del Rey. Sun-Fri. 40 hrs. $425. Contact: UCLA Department of Radiological Sciences.

(Continued on Page 627)

(Continued from Page 626)

April 18-23—**13th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 39 hrs. $445. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 24—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8.25 hrs. $135. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

SURGERY

January 8-9—**15th Annual Postgraduate Course: What's New in General Surgery.** UCD at Hyatt Regency, Sacramento. Fri-Sat. 15 hrs. $285. Contact: UCD.

January 24-29—**16th Annual Postgraduate Assembly in Surgery.** UCSD at Doubletree Hotel, Horton Plaza, San Diego. Sun-Fri. Contact: UCSD.

March 17-20—**Surgical Challenges of the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at CMG Building, La Jolla. Wed-Sat. Contact: UCSD.

May 11-13—**8th Annual Neurosurgery Postgraduate Course: Intracranial Tumors—Modern Management.** UCSF at Grand Hyatt on Union Square. Tues-Thurs. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

December 24-29—**Advances in Medicine '92.** Hawaii Medical Association at Kaanapali Beach, Maui, Hawaii. Fri-Wed. 16 hrs. $450. Contact: Joe Harrison, MD, PO Box 833, Makawao, HI 96768. (808) 878-7657.

January 8-10—**The Medical Office Laboratory Conference.** SDSU at San Diego Red Lion Hotel, Fri-Sun. 20 hrs. $425. Contact: Anne Wright, (619) 594-6255.

January 22-23—**Nutritional Medicine in Medical Practice: Putting Nutrition to Work in the Prevention and Treatment of Common Diseases and Chronic Conditions.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Sat. 14 hrs. $165. Contact: UCLA Extension.

February 5-10—**61st Annual Postgraduate Convention.** Loma Linda Alumni Association at Campus. Fri-Wed. 32.5 hrs. Contact: Alumni Association, LLU, 11245 Anderson St, Loma Linda 92354. (714) 824-4633.

February 22-26—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

March 19-20—**Annual Clinical Nutrition.** UCD at Berkeley Marina Marriott. Fri-Sat. Contact: UCD.

March 26-April 4—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. 1½ wks. Contact: UCLA Extension.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology and Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 11-15—**Twenty-Fourth Annual Cardiovascular Conference at Snowmass.** American College of Cardiology at the Convention Center, Snowmass Resort, Snowmass. Mon-Fri. Contact: Margaret Sgro, American College of Cardiology, (800) 257-4739.

Mericos Eye Institute
Scripps Memorial Hospitals
La Jolla, California

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ALFRED SOMMER, M.D., MHS

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- Phaco Small Incision and Solid State Laser Wet Labs
- Excimer Laser Update with Patient Presentations
- Accredited Technician Program
- Neuro-Ophthalmology Update

FEBRUARY 26th & 27th, 1993

12 Hours of Category 1 CME credit offered.

Limited Enrollment

Contact: SHEILA SEID - (619) 974-6780

January 22-24—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs Medical Center at Beaver Run Resort and Conference Center, Breckenridge. Fri-Sun. Contact: Victoria Hall or Karen Babcock, (303) 393-2826, or FAX (303) 393-4656.

January 23-30—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Tamarron Resort, Durango. Sat-Sat. Contact: U of Colo.

February 22-26—**Colorado Conference on Contemporary Family Practice.** University of Colorado School of Medicine at Breckenridge. Mon-Fri. Contact: U of Colo.

February 27-March 5—**Colorado Review of Anesthesia.** University of Colorado School of Medicine at Vail. Sat-Fri. Contact: U of Colo.

February 27-March 6—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Sat. Contact U of Colo.

February 28-March 5—**ENT Ski Conference.** University of Nebraska Medical Center Continuing Medical Education Program at Keystone Resort, Keystone. Sun-Fri. Contact: Brenda C. Ram, University of Nebraska Continuing Education, (402) 559-4152.

March DTBA—**Fifth Annual Colorado Geriatrics Overview.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. Contact: U of Colo.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

(Continued on Page 628)

(Continued from Page 627)

IDAHO

February 19-21—**Ada County Medical Society's 34th Annual Medical Winter Clinics—"Sandbox Summit"—A Potpourri of Pediatric Pearls.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, Idaho Medical Association members; $175, non-members. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930, or Marie Chester, (208) 386-2135.

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 14-15—**New Mexico Medical Society Annual Meeting.** Society Office, Albuquerque. Fri-Sat. Contact: NMMS, 7770 Jefferson, Ste 400, Albuquerque 87109. (505) 828-0237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 14—**Pediatric Topic.** Thurs. Contact: UOS.

January 26-30—**Craniofacial/Oculoplastic Surgery.** UUSM at Cliff Lodge, Snowbird. Thurs-Sat. 21 hrs. $475. Contact: UUSM.

February 8-12—**Advances in Internal Medicine.** UUSM at Snowbird, Mon-Fri. Contact: UUSM.

February 8-12—**Surgical Pathology.** UUSM at Yarrow Hotel, Park City. Mon-Fri. 20 hrs. $495. Contact: UUSM.

February 12-13—**Utah Ophthalmology Society—Annual Winter Ski Meeting—Ski '93.** Fri-Sat. Contact: UOS.

February 13-20—**Update in Clinical Microbiology and Immunology.** UUSM at Yarrow Hotel, Park City. 1 wk. 25 hrs. $435. Contact: UUSM.

February 19-23—**37th Anesthesiology Update: Anesthesia and the Nervous System.** UUSM at Snowbird Cliff Lodge. Fri-Tues. 20 hrs. $500. Contact: UUSM.

February 23-27—**Physical Medicine and Rehabilitation Update.** UUSM at Prospector Square Conference Center, Park City. Tues-Sat. 16 hrs. $350. Contact: UUSM.

February 28-March 3—**33rd Annual OB/GYN Update.** UUSM at Yarrow Hotel, Park City. Sun-Wed. 13 hrs. $375. Contact: UUSM.

March 3-6—**Maternal Fetal Medicine Update Course.** UUSM at Yarrow Hotel, Park City. Wed-Sat. 13 hrs. $375. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** UUSM at University Park Hotel, Salt Lake City. Mon-Fri. 30 hrs. $1,900. Contact: UUSM.

March 8-12—**Advances in Internal Medicine.** UUSM at Cottonwood Center, Snowbird. Mon-Fri. 20 hrs. $375. Contact: UUSM.

March 12-13—**Western Intermountain Neurological.** UUSM at University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

March 23-26—**Family Practice Refresher Course.** UUSM at Salt Palace, Salt Lake City. Tues-Fri. 27 hrs. $450. Contact: UUSM.

April 2—**Nephrology and Hypertension.** UUSM at University Park Hotel, Salt Lake City. Fri. 7 hrs. $50. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

(Continued on Page 629)

(Continued from Page 628)

December 15-16—**Introduction to Industrial Hygiene.** Seattle. Tues-Wed. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 7—**Community Air Quality.** Seattle. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

January 15-17—**WTS Chest Conference and Lung Day.** Leavenworth. Fri-Sun. Contact: Washington Thoracic Society, (206) 441-5100.

January 21—**Law and Medicine Symposium.** Seattle. Thurs. Contact: PCMS CME.

January 21-22—**Alzheimer's Update.** Seattle. Thurs-Fri. Contact: U/W.

January 27—**Oncology Update.** Tacoma. Tues. Contact: Multicare, (206) 594-1221.

January 29—**Psycho-social and Neuropsychiatric Aspects of AIDS.** Seattle. Thurs. Contact: U/W.

February 3—**HIV Infections.** Tacoma. Wed. Contact: PCMS CME.

February 4-6—**Mt. Bachelor—CME.** Bend, Oregon. Thurs-Sat. Contact: PCMS CME.

February 11—**Managing Occupational Health and Safety Programs.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

February 12—**General Surgery Review.** Everett. Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

February 19—**Healthcare Economics in the '90s.** Seattle. Fri. Contact: VMMC.

February 26—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

February 26-27—**Gastroenterology Update.** Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine, (509) 448-2513.

March 2—**Health Effects of Noise Exposure.** Seattle. Tues. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 3-6—**North Pacific Pediatric Society.** Seattle. Wed-Sat. Contact: Children's, (206) 526-2501.

March 11—**Neurotoxicology.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 11-12—**Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 12—**Pulmonary Medicine for the Family Practitioner.** Seattle. Fri. Contact: Children's, (206) 526-2501.

March 15-25—**Physical Medicine and Rehabilitation Review.** Seattle. Mon-Wed. Contact: U/W.

March 19-20—**APLS Course.** Seattle. Fri-Sat. Contact: Washington Chapter, American College of Emergency Physicians.

March 24-26—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 26-27—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: Washington Academy of Eye Physicians and Surgeons, (206) 441-9762.

March 31—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

April 6-9—**Family Practice Review.** Arizona. Tues-Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

April 8-9—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

April 9—**Advances in Occupational and Environmental Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 16—**20th Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 16-17—**Tacoma Surgical Club.** Tacoma. Thurs-Fri. Contact: PCMS CME.

April 23—**Terminal/Palliative Care Update.** Tacoma. Fri. Contact: PCMS CME.

April 23-24—**Clinical Allergy for the '90s.** Seattle. Fri-Sat. Contact: VMMC.

April 23-25—**Washington State Physical Therapy Association.** Seattle. Fri-Sun. Contact: Children's, (206) 526-2501.

April 28-30—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Fri. Contact: Washington Chapter, American College of Emergency Physicians, (206) 441-9762.

April 30-May 2—**Radiology Annual Meeting.** Vancouver, BC. Fri-Sun. Contact: Pacific Northwest Radiological Society, (206) 441-9762.

May 7—**Office Gynecology.** Tacoma. Fri. Contact: PCMS CME.

May 7-8—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

May 13—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 14-15—**Northwest Spine Review Course.** Seattle. Fri-Sat. Contact: VMMC.

May 16-19—**American Thoracic Society.** San Francisco. Sun-Wed. Children's, (206) 526-2501.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare, (206) 592-1221.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact. U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

February 18-20—**Wyoming Medical Society—Winter Seminar.** Holiday Inn at Gillette. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. ◆

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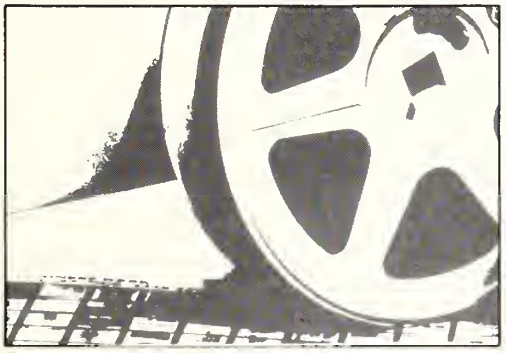

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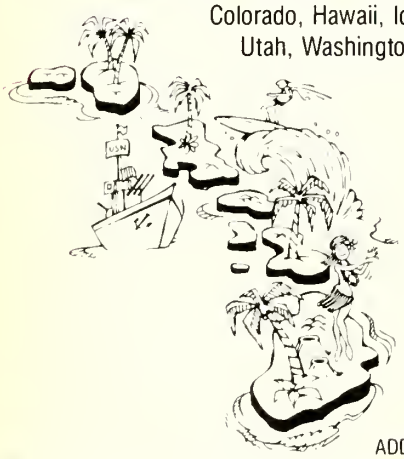

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Biomedical Science

Future Prospects for Treatment of Hemoglobinopathies

JOHN A. STAMATOYANNOPOULOS, *Seattle, Washington*

This paper was chosen as the winner of THE WESTERN JOURNAL OF MEDICINE *'s 1992 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and will be repeated annually.*

LINDA HAWES CLEVER, MD
Editor

Strategies for the treatment of sickle cell anemia and β-thalassemia are founded on the knowledge that these disorders result from structural or functional defects in an adult gene for which an intact fetal counterpart exists. During the past decade, several pharmacologic agents have been investigated for their potential to ameliorate sickle cell anemia and β-thalassemia by increasing the synthesis of fetal hemoglobin in adults. Progress in understanding globin gene regulation is now being combined with advances in retrovirus-mediated gene transfer, and the once-distant goal of providing gene therapy for hemoglobinopathies is rapidly approaching reality.

(Stamatoyannopoulos JA: Future prospects for treatment of hemoglobinopathies. West J Med 1992 Dec; 157:631-636)

The quaternary structure of adult hemoglobin (Hb A) comprises four polypeptide subunits, two α-globin chains and two β-globin chains ($\alpha_2\beta_2$).[1] The α chains are encoded by a gene locus on chromosome 16, and the β chains arise from a similar locus on the short arm of chromosome 11 (Figure 1).[1] The β-globin gene locus contains a number of different genes encoding β-like gene products that are arrayed on the chromosome in a 5′ to 3′ manner that indicates the order of their expression during development. These include an embryonic globin gene (ε), duplicated fetal genes (γ), and adult genes (δ and β). During fetal life, γ-globin is the predominant β-like globin product, giving rise to a fetal hemoglobin (Hb F) containing two α and two γ chains ($\alpha_2\gamma_2$). Around the time of birth, γ-globin production declines precipitously and is replaced by the definitive β-globin gene product, with a corresponding production of adult hemoglobin (Hb A; Figure 2). As such, any structural or functional defects that affect the β-globin gene become clinically evident only on completion of the perinatal γ- to β-globin switch.[1]

During the past decade, a wealth of information concerning the regulation of hemoglobin switching has come to light, much of which is beyond the scope of this review. For our purposes it will be sufficient to note the following:

- Globin genes are regulated at the transcriptional level through the interaction of tissue-specific and ubiquitous transcriptional factors.[2]
- The mechanism of fetal-to-adult gene switching within the β-globin locus appears to involve competition between the γ and β genes for enhancer sequences clustered loosely in a region 6 to 22 kilobases "upstream" (5′) of the embryonic ε gene, designated the locus control region (LCR; see Figure 1)[3,4]; and
- The chronology of hemoglobin switching during gestation appears to be under the control of a developmental "clock" local to chromosome 11 because individual chromosomes isolated from fetal-stage erythroblasts (through hybridization with mouse erythroleukemia cells) undergo temporally correct switching in culture.[5]

Whereas the embryonic ε-globin gene is rendered transcriptionally inert early in gestation, γ-globin production persists at a low level following the fetal-to-adult switch.[1] In consequence, Hb F is found to comprise about 1% of the hemoglobin in normal adults. Its distribution, however, is restricted to a small subset (0.2% to 7%) of erythrocytes, designated F cells, where it accounts for roughly 15% to 20% of their intracellular hemoglobin. How exactly Hb F in adults

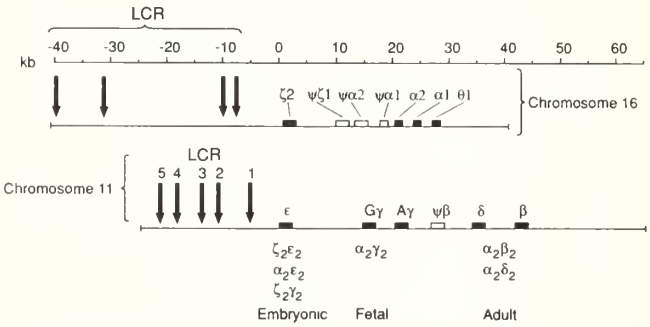

Figure 1.—The human globin genes are shown. Both β- **(top)** and α- **(bottom)** gene clusters contain developmentally controlled genes (see Figure 2). Several kilobases (kb) "upstream" (5′) of each gene cluster are sequences (locus control regions [LCR]) crucial for tissue-specific high-level expression. Important sequences are localized by the presence of DNA hypersensitive to digestion by nucleases, indicating an active chromatin conformation **(large arrows)**. Similar hypersensitive sites are found in the promoter regions of active genes.

comes to be sequestered heterocellularly is not known, but the available evidence can be explained under a model encompassing the kinetics of erythropoiesis.[6] The earliest identifiable erythroid progenitor is the burst-forming unit-erythroid (BFU-E). During normal erythroid maturation, BFU-Es give rise to erythropoietin-sensitive colony-forming progeny, the colony-forming unit-erythroid (CFU-E). After an indeterminate period of time, CFU-Es commit irrevers-

From the University of Washington School of Medicine, Seattle.
Reprint requests to John A. Stamatoyannopoulos, 3336 Cascadia Ave S, Seattle, WA 98144.

ABBREVIATIONS USED IN TEXT

BFU-E = burst-forming unit-erythroid
CFU-E = colony-forming unit-erythroid
Hb = hemoglobin
LCR = locus control region

ibly to the terminal maturation pathway, and globin synthesis accelerates dramatically. An intriguing feature of erythropoiesis in the adult is the retention by many early erythroid-lineage cells (BFU-Es and CFU-Es) of what appears to be an immature globin "program."[6] During normal terminal maturation with its increasing globin synthesis, a distinct intracellular transition from fetal to adult globin production ensues. F cells in the adult presumably derive from progenitor cells

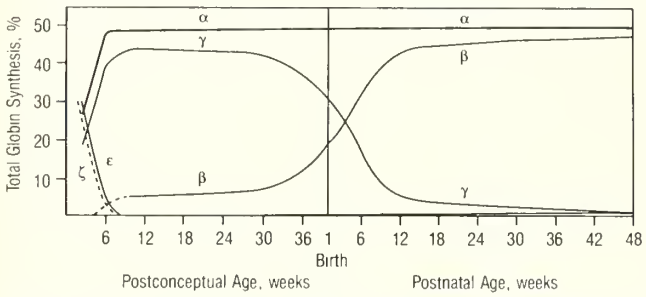

Figure 2.—Globin gene expression is shown during development. Embryonic ζ and ϵ genes are extinguished early in gestation. α-Globin expression remains roughly constant following the disappearance of ζ, whereas γ- and β-globin genes are expressed in a more reciprocal pattern.

that enter terminal maturation prematurely and fail to inactivate completely their primitive globin programs. F-cell numbers increase in response to erythropoietic stress such as that induced by acute anemia or following bone marrow transplantation or the application of cytotoxic drugs.

Inherited Disorders Affecting Hemoglobin

Sickle cell anemia and β-thalassemia are inherited disorders of hemoglobin structure and synthesis, respectively, that have their origins in mutations affecting the β-globin gene locus. Each year, about 160,000 persons worldwide are born destined to have clinical disease associated with these disorders. Many more persons inherit mutations affecting the α-globin gene locus (α-thalassemia),[7] but their condition is usually clinically mild and will not be discussed in this review.

In sickle cell anemia, a point mutation in the DNA sequence of the β-globin gene yields a variant polypeptide containing valine at position 6 in place of the wildtype glutamic acid.[1] The resulting globin protein (designated β^S) complexes with another of its kind and two α globins to form a hemoglobin variant (Hb S) with anomalous physical properties. In its deoxy form, Hb S undergoes spontaneous polymerization; the mechanics of polymer elongation involve a generation of oblique forces on the cell membrane with consequent severe distortions in red cell morphology (yielding ultimately the characteristic "sickle" shape), membrane damage, and a substantial loss of plasticity. On deoxygenation during traversal of the microvasculature, Hb S-containing cells undergo progressive stiffening, which may precipitate the occlusive crises that underlie the clinical manifestations of this disease. In addition to episodic pain crises, patients with sickle cell disease suffer from an acute extravascular hemolysis of Hb S-containing cells by the mononuclear phagocytic system. No effective conventional therapies for sickle cell anemia exist, and treatment of this disorder is confined to the management of acute pain crises and the consequences of end-organ damage.

β-Thalassemia is characterized by deficient or absent production of β-globin chains.[8] This condition may arise from various mutations including lesions that alter grossly the structure of the β-globin gene or remove it altogether; mutations in the β-globin promoter that substantially inhibit transcriptional activity; and point mutations in the β gene that have an adverse effect on subsequent messenger RNA processing (through the activation of cryptic splice or donor junctions) or on translation (frameshift mutations).[9] An impairment of β-gene function results in a considerable decline in total hemoglobin production, and accumulated excess α-globin chains form intracellular precipitate aggregates that promote cell lysis and destruction by host-defense mechanisms.[8] The vast majority of these cells are vanquished before they exit from the marrow compartment, resulting in a markedly ineffective erythropoiesis and a severe anemia; those that make their way into the peripheral blood display profound microcytosis and other red cell deformities. In compensation for this condition, erythropoiesis expands dramatically, resulting in a hyperplastic marrow with adverse consequences for developing bones.

Patients with homozygous β-thalassemia require periodic transfusions to maintain vitality, but the onset of iron overload ensures mortality in most by the third decade of life. Current approaches to transfusion therapy involve the coadministration of iron chelators such as deferoxamine, which results in prolonged life expectancy.

Persistence of Fetal Hemoglobin in the Adult Ameliorates Sickle Cell Anemia and β-Thalassemia

Several lines of evidence point to the conclusion that increasing cellular levels of Hb F should prove clinically beneficial to sufferers of sickle cell anemia and β-thalassemia. A number of mutations have been characterized that underlie the hereditary persistence of fetal hemoglobin in adulthood. Persons showing high levels of fetal hemoglobin (10% to 40% in heterozygotes; 100% in homozygotes) are clinically asymptomatic and show normal exercise tolerance.[1]

Studies of compound heterozygotes for sickle cell disease and the hereditary persistence of fetal hemoglobin have revealed that levels of Hb F exceeding 20% are associated with a mild or benign clinical course. Other reports indicate that protection from severe end-organ damage may occur with Hb F values in the range of 10%, and the results of a recent study involving several thousand sickle cell patients observed over a period of years indicate that even small increases in fetal hemoglobin levels can have important long-term effects on disease morbidity.[10]

The role of fetal hemoglobin in sickle erythrocytes has been studied extensively.[11] Because the rate of Hb S polymerization depends strongly on its intracellular concentration, increasing the proportion of nonsickle hemoglobins within a particular cell through the increased production of fetal hemoglobin ($\alpha_2\gamma_2$) and a mixed tetramer containing one β^S chain and one γ chain ($\alpha_2\gamma\beta^S$) will shift reaction kinetics away from polymer formation. A more important finding is that Hb F has a profound direct inhibitory effect on polymer formation, and mixed tetramers containing a γ chain do not

participate in polymer formation. With respect to polymerization potential, the effect thus brought about directly by Hb F can be expressed in terms of a decline in Hb S concentration, such that a 10% increase in intracellular fetal hemoglobin has a "sparing" effect equivalent to a 10% decline in hemoglobin concentration. Because the kinetics of polymerization vary with the 30th power of deoxy-Hb S concentration, even modest changes in this index can have a major influence on polymer formation.

In the case of β-thalassemia, any increase in the production of non-α-globin genes will result in a more effective erythropoiesis.[8] Substantial amounts, however, of fetal hemoglobin tetramers would be required before clinical effects could be expected to be alleviated. Thalassemia in patients who have inherited a mutation for the hereditary persistence of fetal hemoglobin generally remains clinically benign.

Therapeutic Strategies for Hemoglobinopathies

Although sickle cell anemia and β-thalassemia have a common origin in mutations affecting the β-globin gene, their pathophysiologies dictate a fundamentally different approach to the treatment of each disorder. In β-thalassemia, total β-like globin synthesis is deficient, and hence notable production of any non-α-globins will prove beneficial. This can be achieved either through the activation of high levels of fetal hemoglobin synthesis in an adult or through the production of adult hemoglobin (Hb A) potentiated by the presence of a high-expressing retrovirally introduced β-globin gene.

In sickle cell disease, globin production is adequate; the function of an optimal therapeutic agent would therefore be directed toward the inhibition of Hb S polymerization. The retroviral introduction of a normal β-globin gene would counter the detrimental effects of Hb S only indirectly through a reduction of the intracellular fraction of Hb S. Unlike Hb F, however, Hb A copolymerizes to a limited extent with Hb S, and mixed tetramers ($\alpha_2\beta^S\beta$) enter readily into elongating polymers. The greater sparing effect conferred by Hb F thus dictates that a retrovirally transduced γ-globin gene would prove to be a far more optimal therapy for sickle cell disease and would have the advantage of requiring relatively low levels of cellular expression to achieve a beneficial functional outcome.

Pharmacologic Stimulation of Hemoglobin F Synthesis

To date, several pharmacologic agents have shown a capacity for meaningfully increasing Hb F synthesis in both humans and nonhuman primates.[12] These include cell-cycle–specific cytotoxic compounds, nucleoside analogues, hematopoietic growth factors, and butyric acid derivatives. Four drugs have been subjected to clinical trials of varying scope: the cytosine analogue 5-azacytidine; hydroxyurea, a well-characterized cytostatic agent that blocks DNA replication through the inhibition of the ribonucleoside diphosphate reductase enzyme complex; erythropoietin, the principal growth factor of the erythroid lineage; and sodium butyrate. Furthermore, synergistic activity has been observed when certain combinations of these agents are used.

The application of the aforementioned agents with the aim of stimulating fetal hemoglobin synthesis in patients suffering from hemoglobinopathies has recently been reviewed in detail.[12] Patients with sickle cell disease to whom single courses of 5-azacytidine were administered as intravenous infusions have increased their genetically determined baseline levels of Hb F fourfold to sevenfold.[13-16] Observed rises in Hb F levels have been paralleled by decreases in the synthesis of Hb S, and absolute fetal hemoglobin concentrations in the range of 6% to 18% have been recorded. Similar gains have been achieved using single-course treatments in patients with β-thalassemia, with consequent transient improvements in the quality of erythropoiesis.[17-20] As in the case of patients with sickle cell anemia, increases in Hb F were accompanied by decreases in the synthesis of adult hemoglobin, thus compromising the final hemoglobin concentration and hence overall therapeutic efficacy.

The ability of hydroxyurea to produce increases in Hb F in sickle cell patients has been documented by studies in nearly 80 patients. The daily administration of hydroxyurea in doses that do not give rise to meaningful myelosuppression (10 to 30 mg per kg per day) has produced increased Hb F levels in nearly every case, with most patients achieving peak absolute Hb F levels of 5% to 15%, and some patients exceeding 20%.[21-23] In addition to its effect on Hb F, hydroxyurea therapy produces changes in the mean cell volume and the mean corpuscular hemoglobin concentration that result in substantial reductions in circulating dense and irreversibly sickled cells; the effect of these changes on the rheologic properties of erythrocytes should complement the effect of Hb F on disease morbidity. There is preliminary evidence that patients with sickle cell anemia on long-term hydroxyurea therapy have a decreased incidence of painful crises.[23]

A handful of sickle cell patients treated with recombinant human erythropoietin alone (1,000 to 2,000 U) have responded with modest increases in fetal hemoglobin synthesis that appear to be dependent on the coadministration of iron supplements.[24,25] These gains, however, combined with the potentially detrimental effects of an erythropoietin-induced erythrocytosis in sickle cell disease, all but ensure that this drug will not be used by itself as a therapeutic agent for hemoglobinopathies. Recent studies in patients with sickle cell disease, however, have shown that administering erythropoietin in combination with hydroxyurea therapy using an alternating dose schedule (4 days of hydroxyurea, 3 days of erythropoietin) can increase considerably the Hb F response elicited by hydroxyurea alone, producing twofold or greater augmentations in some cases.[26] If the magnitude of these increases proves to be a consistent phenomenon, the additional expense of treatment with recombinant erythropoietin will prove more than justified, particularly if its synergy with hydroxyurea can be translated into further reductions in crisis frequency.

Administering sodium butyrate to nonhuman primates has produced strong Hb F responses.[27,28] Moreover, this compound and other butyrate analogues have proved capable of inducing fetal gene activity in cultured populations of erythroid progenitors from patients with thalassemia and those with sickle cell disease.[29] The induction of Hb F in vivo has recently been shown in a few patients with sickle cell disease or thalassemia.[30]

The use of the aforementioned agents has been motivated by observations bearing on factors that affect globin gene regulation during development and erythroid maturation. For example, 5-azacytidine was first used specifically for its effect on DNA methylation. In normal chromatin, DNA is methylated; the pattern of methylation is not random but correlates to some degree with gene activity. This correlation

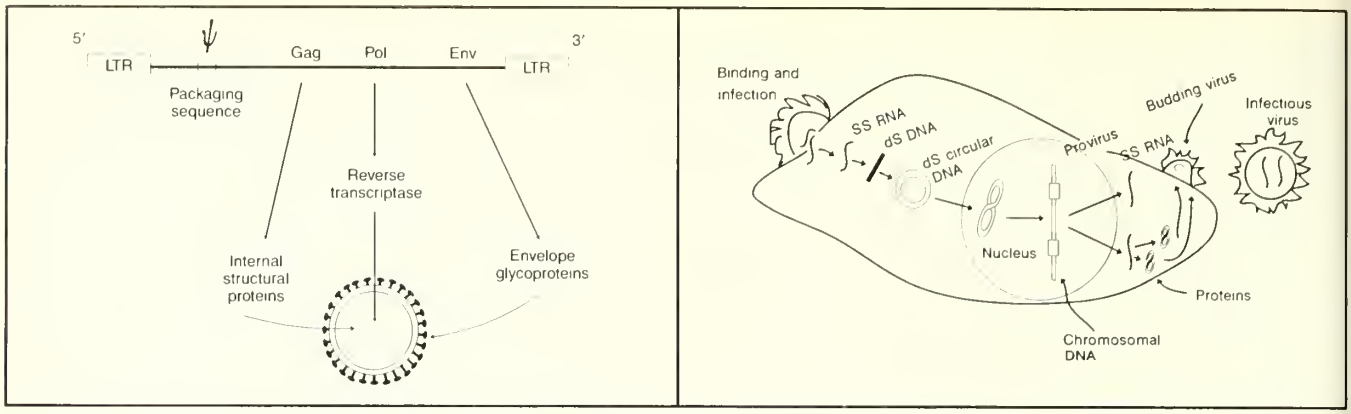

Figure 3.—**Left,** retroviral structure is shown with, **Right,** retroviral life cycle. Removing the ψ packaging signal interrupts the retroviral life cycle, abrogating its ability to assemble infective virions while retaining replication competence (see also Figure 4). Note that retroviral integration into the host genome can occur only during the S phase. LTR = long terminal repeat

was first observed in the β-globin cluster, where it was discovered that the γ-globin genes were demethylated in fetal-stage erythroblasts (where they express at a high level) but heavily methylated in adult-stage erythroblasts (where they are virtually quiescent).[31] These observations suggested immediately that γ-gene reactivation in the adult might be actualized, or at least potentiated, by the application of 5-azacytidine, a cytosine analogue known to effect a global decline in genomic DNA methylation status after being incorporated into replicating DNA, presumably through the interactive inactivation of DNA methyltransferase.

The observation that Hb F synthesis was increased during conditions of accelerated or altered erythropoietic kinetics, combined with the knowledge that the high mitotic rate of maturing erythroblasts made them particularly susceptible to the action of cell-cycle-specific cytotoxic drugs, raised the possibility that a proper application of such agents might be capable of manipulating erythroid kinetics in such a way as to produce a sustained Hb F response.[6] To this end, a number of such agents have been applied in studies using animals and in acute-phase trials, of which only hydroxyurea (because of its low toxicity and ease of administration) has been studied on a long-term basis. Recombinant human erythropoietin was initially administered in an effort to alter erythroid kinetics without cytostatic effects.

The application of sodium butyrate was prompted by the discovery that butyric acid metabolites were present in abnormally high levels in both diabetic women and their newborn children, the latter of whom had considerably delayed fetal-to-adult hemoglobin switching.[32] Subsequently, sodium butyrate was shown in a developing ovine model to be capable of retarding or suppressing completely the switch to adult hemoglobin production.[33]

The mechanisms by which these and other agents produce their effect on Hb F remain the subject of considerable debate. Although largely amibiguous with respect to any particular agent, the evidence to date appears to argue for a mechanism involving manipulation, kinetic or otherwise, of the cellular or maturational clock of hemoglobin switching.

Gene Therapy for Hemoglobinopathies

Human and animal retroviruses are RNA-based organisms that encode a reverse transcriptase activity, which in turn potentiates host genome integration through an intermediate DNA provirus. Retroviruses are propagated by host DNA replication, transcription, and translation machinery that provide for the packaging of viral RNA in a protein coat and its subsequent encapsulation and "budding" in a phospholipid exosome derived from the host plasma membrane (Figure 3).

By manipulating retroviruses with recombinant DNA technology, exogenous DNA fragments can be inserted into the viral genome.[34] Through the selective retention of retroviral sequences responsible for the reverse transcription process and efficient encapsidation, as well as appropriate viral transcription signals located in the long terminal repeats of most retroviruses, it has become possible to engineer replication-incompetent viruses that retain their infective potential (Figure 4). Such manipulations can result in the generation of a novel species that functions effectively as a vehicle for the transfer of desired DNA sequences into the genome of a target cell population susceptible to infection by the virus. Gene therapy aims to harness the power of retrovirus-

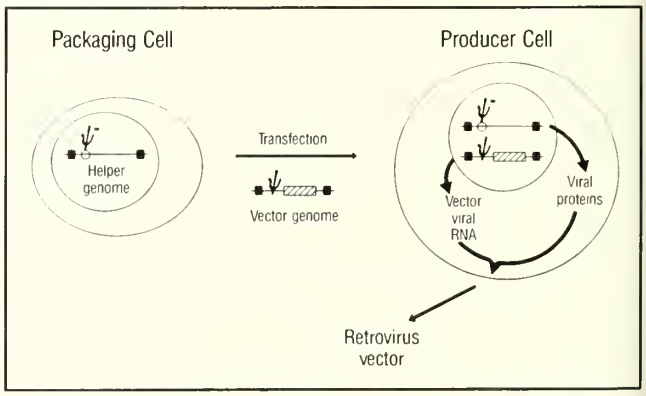

Figure 4.—The production of infective particles containing retroviral vectors is shown. Helper cells infected with ψ- viruses are cotransfected with packaging-competent but replication-incompetent retroviruses serving as vectors for the transfer of exogenous DNA sequences. The coculture of amphotropic and ecotropic packaging cell lines results in superinfection and the production of high virus titers ("ping-pong" strategy).

mediated gene transfer to correct genetic diseases by introducing nondefective gene copies or other genes that may aid in retarding the pathogenesis of a particular disease process.

Assuming the availability of suitable retroviral vectors, current gene therapy protocols for hemoglobinopathies involve autologous bone marrow transplantation. Marrow is removed from a patient, cultured in media containing hema-

topoietic growth factors necessary for the proliferation of progenitor cells, subjected to infection by retroviral particles harvested from the supernatant of a producer cell line, and reintroduced into the patient, who has undergone irradiation in the intervening period (Figure 5).

Several groups have reported successful gene transfer into murine and nonhuman primate hematopoietic stem cells, although obstacles remain to be surmounted before this technology becomes feasible for application in humans. Principal difficulties include the low efficiency of gene transfer into target cells and the low level of expression of exogenous DNA sequences once transfer has been achieved.

Inefficient Gene Transfer

The long-term efficacy of gene therapy in the treatment of hemoglobinopathies is contingent on successful gene transfer into totipotent hematopoietic stem cells. Because these cells make up only a minute fraction of marrow progenitors,

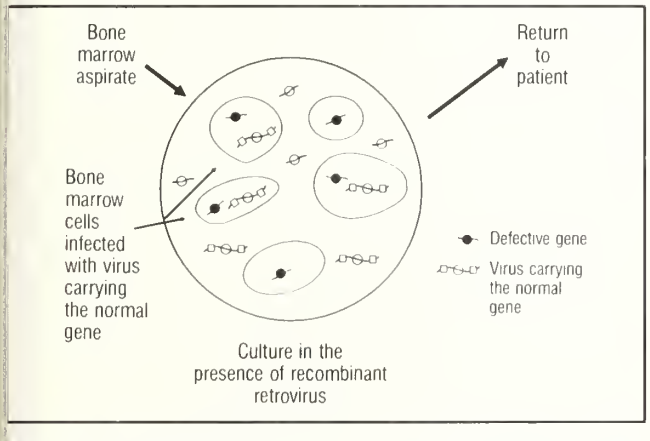

Figure 5.—The diagram illustrates gene therapy for hemoglobinopathies. Bone marrow aspirate containing hematopoietic stem cells is cultured in media replete with infective retrovirus vectors and a complement of hematopoietic growth factors. The latter increases the proportion of stem cells undergoing DNA synthesis and hence increases the infective efficiency of the virus. Infected cells are subsequently returned to the patient by intravenous infusion, whereupon they circulate, lodging once again in the marrow compartment.

the efficiency of gene transfer is correspondingly low. As such, high titers of infectious virions need to be achieved in producer cell lines. Furthermore, because viral integration into a host genome is dependent on DNA replication, the efficiency of gene transfer is compromised severely because stem cells are presumed to be largely quiescent.

Preliminary strategies for overcoming these obstacles have been developed.[35] To increase the production of viral particles by conventional producer cell lines, a "ping-pong" coculture technique has been used wherein ecotropic and amphotropic producer cell lines are combined within the same culture medium, with the result that both cell types become superinfected (> 10 copies of provirus per genome) by one another. From this mixture, a cell line producing roughly 10^9—versus $< 10^6$ for conventional producer lines—replication-competent virus particles per milliliter can be isolated. Viral supernatants derived from such cell lines have enabled highly efficient gene transfer into stem cells capable of long-term, multilineage repopulation following irradiation in both small and large animal models.[35]

Because retroviruses employ host DNA replication machinery to effect integration, target cells must be actively replicating their DNA at the time of infection for stable gene transfer to take place. A number of hematopoietic growth factors have demonstrated a capacity to stimulate the proliferation of multipotent hematopoietic progenitors in vitro, but no one factor appears capable of effecting widespread recruitment of this primitive cell type from quiescence. A systematic examination of several growth factors in both cultures of murine progenitors and lethally irradiated mice has revealed that interleukin 3, when used in combination with interleukin 6, mobilizes stem-cell proliferation and substantially enhances the efficiency of retrovirus-mediated gene transfer.[36] These results should prove extensible to large animal and human models.

Deficient Expression of Exogenous DNA

For effective gene therapy, most retrovirally transduced genes must be expressed at levels approximating those of endogenous genes. This is particularly relevant for sickle cell anemia, where the expression of a transduced globin gene would have to be of such a level as to overcome the deleterious effects of the highly expressed chromosomal β^S gene.

Encapsulation and packaging of retroviral vectors by producer cell lines place severe restrictions on the size of exogenous DNA fragments that can be carried by the vector. This restriction, often referred to as the packaging limit, necessitates that the sequence information required for the tissue-specific, high-level expression of a particular introduced gene fragment be delineated to determine the most efficient combination of enhancer sequences. Most genes contain within their promoter regions transcription information that is actualized by transcriptional factors in the nuclear environment. Transfection studies, however, have shown that promoter sequences alone are generally insufficient to direct the high-level expression of their associated gene. Such expression requires the presence of appropriate enhancer elements, but even when they are present problems remain because enhancers are themselves subject to dampening effects that vary according to their position in the genome. Apparently the chromatin in large regions of the genome is "inactive" in certain tissue types, and exogenous DNA sequences that have integrated into such regions remain transcriptionally inert. Because retroviral integration occurs at essentially random locations throughout the host genome, the expression of DNA sequences introduced into mammalian tissues will be subject to these "position effects." Because of the inherently low efficiency of gene transfer, optimal enhancer elements for gene therapy will need to ensure a position-independent, high-level expression of linked genes while maintaining tissue-specificity. With respect to the β-globin gene, such an element has been delineated.[37]

The high-level expression of globin genes in erythroid tissues is made possible by sequence information contained within the locus control region.[38] When linked to a β-globin gene, the LCR is also able to overcome position effects. Insufficient data exist for this conclusion to be extended to the γ genes. Systematic deletions have pinpointed the precise location of powerful enhancer elements within the LCR that function optimally in conjunction with a linked β-globin gene. In its native state on the chromosome, the LCR occupies roughly 20 kb of DNA.[37] Using the aforementioned deletion data, recombinant constructs spanning only 2 to 3 kb have been assembled; these constructs can direct the expression of a linked β-globin gene in either erythroleukemic cell

lines or transgenic mice to a level approaching that obtained with linkage to the wildtype LCR.[37,39]

Unfortunately, even such reduced constructs are too large to be incorporated, along with linked genes, into properly functioning retroviral vectors. These fragments, however, comprise several enhancer sequences, two of which, when used individually, are capable of delivering roughly half the activity of the entire LCR, thus reducing the size of an efficient β-globin enhancer to only a few hundred base pairs.[40] Such minimal enhancer sequences, when combined with a linked β-globin gene (including its flanking 3′ and 5′ sequences that have been shown to be important for correct expression) are well within the packaging limits of most retroviral vectors. The long terminal repeats of a number of retroviruses are known to contain "silencer" elements, which may abrogate the potency of small recombinant enhancers. Such silencer elements, however, are not expected to have the power to suppress enhancer elements on the scale of the LCR or its fully active recombinant derivatives.

If retroviral packaging limits continue to present difficulties, a more detailed delineation of enhancer elements within the LCR will be needed. The interaction of LCR elements with linked globin genes has thus far been studied primarily in the context of the β gene and is therefore of great value in the construction vectors aimed at gene therapy for thalassemia. For reasons outlined earlier, however, ideal therapy for sickle cell anemia will require the introduction of a γ-globin gene. As such, further information concerning the interaction of this gene with sequences in the LCR may be needed.

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Articles

The Effect of Human Immunodeficiency Virus Infection on the Distribution and Outcome of Pneumonia in Intensive Care Units

KELLY J. TUCKER, MD, *San Francisco;* BETTE ANTON, MLS, *Berkeley; and* HARVEY J. TUCKER, MD, *San Francisco, California*

To determine the frequency and distribution of pneumonia in an intensive care unit (ICU), we retrospectively examined the records of 1,854 consecutive ICU admissions between January 1987 and April 1990. A total of 266 patients met criteria for pneumonia (unilateral or bilateral infiltrate by chest roentgenogram, plus 2 of the following: leukocyte count $>10 \times 10^9$ per liter, temperature $>38.5°C$, or culture of blood or sputum positive for pathogens). *Pneumocystis carinii* pneumonia in patients infected with the human immunodeficiency virus was the most frequent cause (28%) precipitating an ICU admission in this series of patients. *Streptococcus pneumoniae* (13%), *Staphylococcus aureus* (8%), *Haemophilus influenzae* (4%), and viruses (4%) were also commonly observed. Overall mortality was 20%. An APACHE II score of greater than 24, the need for intubation, and the presence of *P carinii* were predictive of increased mortality. Age, sex, and length of stay did not predict final results. Patients with *P carinii* pneumonia who required intubation had an overall mortality of 54%, which was higher than patients without *P carinii* pneumonia who required intubation ($P<.05$).

Our experience shows the changing spectrum of pneumonia in ICUs. In contrast to reports of a decade ago in which *S pneumoniae* and *Pseudomonas aeruginosa* are cited as most common, *P carinii* is now most prevalent in our ICU. Although our findings reflect the increasing incidence of human immunodeficiency virus infection in San Francisco, California, they may also be pertinent to other areas in the United States where the incidence of this infection continues to increase.

(Tucker KJ, Anton B, Tucker HJ: The effect of human immunodeficiency virus infection on the distribution and outcome of pneumonia in intensive care units. West J Med 1992 Dec; 157:637-640)

Pneumonia is a common problem in intensive care units (ICUs), with a reported incidence of 1.5% to 21.6%.[1-3] Despite tremendous advances in antimicrobial therapy and intensive care medicine, mortality due to pneumonia remains an important problem with reported rates of 20% to 53%.[4-7] Although microbiologic and clinical diagnoses of specific causal organisms in cases of pneumonia may be difficult, the most frequent organisms noted are *Streptococcus pneumoniae*, staphylococcal species, and enteric Gram-negative rods. As in many other areas of medicine, the emergence of human immunodeficiency virus (HIV) infection and the consequent acquired immunodeficiency syndrome (AIDS) has profoundly affected the spectrum of pneumonia in intensive care units. Beginning in the mid-1980s, we began to observe a variety of pneumonic illnesses associated with HIV infection. It is now well established that *Pneumocystis carinii* pneumonia is the most common opportunistic infection in patients with AIDS.[8]

We undertook this study to quantitatively assess the effects of the HIV epidemic on the distribution and outcome of pneumonia in intensive care units. Our retrospective analysis includes 266 cases of pneumonia in the intensive care unit of a nonprofit, community-based hospital in San Francisco, California. We report the frequency, distribution, and outcome in this population and discuss the effect of HIV infection on each of these variables. This information should assist clinicians in the decision analysis process when treating patients with pneumonia in an intensive care unit.

Patients and Methods

We retrospectively analyzed the records of 1,854 consecutive ICU admissions at the California Pacific Medical Center between January 1987 and April 1990. In this nonprofit community-based hospital located in San Francisco, California, about 15% of all admissions are related to HIV infection.

All cases of patients admitted to the ICU with a diagnosis of pneumonia or respiratory failure were considered for entry into the study. Only cases subsequently determined to be pneumonia were analyzed. For the purposes of entry into the study, pneumonia was defined as an acute respiratory illness in which unilateral or bilateral infiltration was identified on a chest roentgenogram, plus two of the following: leukocyte count greater than 10×10^9 per liter (10,000 cells per μl), temperature higher than 38.5°C (101.3°F), or a culture of blood or sputum positive for pathogens. A total of 266 patients met the criteria for pneumonia and form the population that underwent analysis. The study was reviewed and approved by the Institutional Review Board at the California Pacific Medical Center.

Demographic and clinical features that were analyzed for

From the Intensive Care Unit, California Pacific Medical Center, San Francisco (Drs Tucker and Tucker), and the Health Sciences Information Service, University of California, Berkeley (Ms Anton).

Financial support for this work was provided by the California Pacific Medical Foundation.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
APACHE = Acute Physiology and Chronic Health Evaluation
HIV = human immunodeficiency virus
ICU = intensive care unit

each patient included age, sex, clinical outcome, results of microbiologic culture, and length of ICU stay.* All physiologic variables required to calculate an APACHE [Acute Physiology and Chronic Health Evaluation] II severity of illness score were collected.[9] APACHE II scores are routinely prospectively calculated on all ICU admissions to our facility.

Bacteriologic cultures of blood and sputum were done according to standard microbiologic techniques. The diagnosis of *P carinii* pneumonia was confirmed by toluidine blue

Figure 1.—The percentage frequency of pneumonia for age shows the bimodal distribution seen in an intensive care unit (ICU) population (n = 266). A younger group is shown with a mean age of 40 years, representing the population infected with the human immunodeficiency virus.

staining of bronchoalveolar lavage fluid or sputum or silver methenamine stain of transbronchial lung biopsy specimens. Whenever it was deemed clinically appropriate, specimens of serum were tested for antibodies to specific viruses, *Legionella pneumophila,* and *Mycoplasma pneumoniae* by complement fixation and indirect fluorescent antibody tests.

Statistical Analysis

Distribution data are presented as absolute values and percentage frequencies. Prognostic variables are presented as means plus or minus a standard deviation for continuous data and proportions for nominal data. The significance of differences between groups was determined using the Student's *t* test (2-tailed, unpaired) for continuous data and χ^2 (2 by 2 with continuity correction) for nominal data. A *P* value of less than .05 was taken as statistically significant.

*Jackie Louie, RN, and Debbie Loundsbury, RN, assisted in collecting patient data.

Results

Of 1,854 patients screened for entry into the study, 266 cases met the inclusion criteria for pneumonia in the ICU, yielding an incidence of 14.3%. Of the 266 patients, 166 were men. Ages ranged from 18 to 98 years with a mean of 60.7 ± 14 years. The percentage frequency polygon for age (Figure 1) reveals a bimodal population with dual peaks at ages 40 and 68 years. Concurrent HIV infection occurred in 39% of cases and tended to occur in younger patients. The APACHE II score ranged from 2 to 46 and correlated well with final results (Figure 2).

Presented in Table 1 is the distribution by pathologic organism in our study population. A definitive cause could be identified by microbiologic or immunologic methods in 79% (210/266). *Pneumocystis carinii* was the most frequent pathogen observed, accounting for 27.8% (74/266) of cases. All patients with *P carinii* pneumonia were also HIV infected. Mortality in this group was 35% (26/74) and rose to 54% (14/26) if mechanical ventilation was required (Table 2). *Streptococcus pneumoniae* was observed in 13.1% (35/266), and 49% (17/35) of these patients had concurrent HIV infection. *Pseudomonas aeruginosa,* staphylococcal species, *Haemophilus influenzae,* and viral pneumonia were also commonly observed. A small number of cases (< 1% each) were caused by mycobacteria, *Legionella* species, *Aspergillus* species, and *Mycoplasma pneumoniae.*

Of the 266 patients, 53 (19.9%) died during their ICU course. The mean APACHE II score in the study population was 20 ± 3.1 points. According to data published by Knaus and colleagues, the mean APACHE II score of our series would yield a predicted mortality of 25%.[10] Comparisons between survivors and nonsurvivors are shown in Table 3. The APACHE II scores were significantly elevated in nonsurvivors ($P < .05$). The need for intubation and mechanical ventilation and the presence of *P carinii* pneumonia and concurrent HIV infection were all more common in nonsurvivors ($P < .05$). There was no difference in age, sex, and length of ICU stay when survivors and nonsurvivors were compared.

TABLE 1.—*Cause of Pneumonia and Outcome*

Organism	*Patients, No. (%)**	*Patients HIV Positive, No. (%)*	*Patients Intubated, No. (%)*	*Mortality, No. (%)*
Pneumocystis corinii	74 (28)	74 (100)	26 (32)	26 (35)
Streptococcus pneumonioe	35 (13)	17 (49)	18 (51)	7 (20)
Pseudomonos oeruginoso	30 (11)	2 (7)	12 (40)	4 (13)
Stophylococcus oureus	20 (8)	0 (0)	10 (50)	4 (20)
Hoemophilus influenzoe	12 (4)	2 (17)	2 (17)	2 (17)
Viral	11 (4)	3 (27)	2 (18)	1 (9)
Indeterminate	56 (21)	6 (11)	18 (32)	6 (11)
Other	28 (10)	0 (0)	4 (14)	3 (11)
Total	266 (100)	104 (39)	92 (34)	53 (20)

HIV = human immunodeficiency virus

*Percentages add up to less or more than 100% because of rounding off.

Discussion

We undertook this study to determine the effect of HIV infection on the distribution and outcome of pneumonia in the ICU. Shown in Table 4 are the results of four previous investigations into the distribution of pneumonia in ICUs identified by a MEDLINE search of the English-language literature back to 1975. In contrast to these reports, in which enteric Gram-negative rods and *S pneumoniae* are cited as the most common organisms, we found *P carinii* to be the most frequent pathogen. Whereas HIV infection was not discussed as an important modifier of the distribution of pneumonia in the ICU in any of these previous reports, we found a strong relationship, with an incidence of concurrent HIV infection equal to 39% in cases of pneumonia in the ICU. In addition to the expected association between HIV infection and *P carinii* pneumonia, we also found a high incidence of HIV infection among cases of bacterial pneumonias. This relationship was especially pronounced in patients with *S pneumoniae* pneumonia of whom 48% (17/35) were also HIV infected. An impaired antigen-specific humoral immune response seen in patients with HIV infection may predispose this population to bacterial infections and would argue in favor of the widespread use of polysaccharide streptococcal vaccines.[11]

TABLE 2.—*Mortality Distribution According to Need for Intubation**

Organism	Patients Intubated, No./No. (%)	Patients Nonintubated, No./No. (%)
Pneumocystis carinii	14/26 (54)†	8/50 (16)
Streptococcus pneumoniae	5/18 (28)	2/17 (12)
Pseudomonas aeruginosa	2/12 (17)	2/18 (11)
Staphylococcus aureus	3/10 (30)	1/10 (10)
Haemophilus influenzae	1/2 (50)	1/10 (10)
Viral	1/2 (50)	0/9 (0)
Indeterminate	2/18 (11)	4/38 (10)
Other	2/4 (50)	2/24 (8)
All non-*P carinii* pneumonia	16/66 (24)	12/126 (10)

*The numerators represent nonsurvivors in each group.
†Intubated patients with *P carinii* pneumonia versus those without, $P<.05$.

TABLE 3.—*Prognostic Factors Related to Outcome*

Clinical Variable	Survivors (n=213)	Nonsurvivors (n=53)
APACHE II, mean±SD	12.9±2.9	22.8±3.8
Intubated, No. (%)	60 (28)	30 (57)*
Pneumocystis carinii pneumonia, No. (%)	48 (22)	26 (49)*
Human immunodeficiency virus, No. (%)	69 (32)	35 (66)*
Age, mean years±SD	66.0±12.0	48.0±10.3
Sex, male/female	133/80	33/20
Length of stay, mean days±SD	11.2±4.3	8.9±3.1

*$P<.05$.

Several possible limitations of this study should be addressed. First and most important, the incidence of HIV infection at our institution may be higher than at similar facilities across the country. The prevalence of HIV infection in San Francisco is among the highest in the nation; however, because incidences of HIV infection are rising at an alarming rate throughout the United States, the distribution of pneumonia in ICUs, as we have observed, should be expected to change in other areas as well. Second, our definition of pneumonia may have excluded patients who actually had pneumonia, but who had leukopenia or hypothermia as one of their clinical manifestations. Conversely, a small number of patients may have met study criteria but did not actually have pneumonia. No definition of pneumonia is perfect. Because provisions are routinely instituted to evaluate fully the origin of pneumonic infiltrates in all patients admitted to the ICU at our institution, these possible limitations would be expected to have only a minimal effect on our overall findings.

Several authors have investigated the effect of HIV infection and AIDS on survival in patients admitted to hospital who required ICU support. Initial studies cited mortality of 85% to 100% among cases of AIDS, *P carinii* pneumonia, and respiratory failure.[12-17] In the past few years more encouraging reports have been published. Hospital survival rates for AIDS patients with respiratory failure are reported as 36% to 50% in these studies.[18-23]

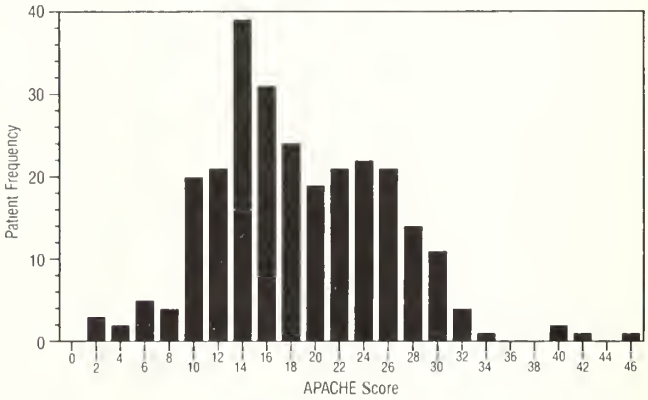

Figure 2.—The Acute Physiology and Chronic Health Evaluation (APACHE II) distribution histogram shows the wide range of acuity index seen in patients with pneumonia requiring support in an intensive care unit.

The overall mortality in our study was 20%, and the APACHE II score accurately predicted the outcome. The subset with the highest mortality was patients with *P carinii* pneumonia who required mechanical ventilation because of

TABLE 4.—*Pneumonia in Intensive Care Units—Comparison With Previous Investigations*

Investigators	Study Size	Cause of Pneumonia: Pneumocystis carinii, No. (%)	Streptococcus pneumoniae, No. (%)	Staphylococcus aureus, No. (%)	Gram-Negative Rods, No. (%)	Indeterminate, No. (%)	Mortality, No. (%)
Feldman et al, 1989[4]	73	0 (0)	26 (36)	3 (4)	23 (32)	16 (22)	39 (53)
Langer et al, 1987[6]	441	0 (0)	95 (22)	34 (8)	112 (25)	199 (45)	88 (20)
Sørensen et al, 1986[5]	30	0 (0)	4 (13)	0 (0)	10 (33)	15 (50)	14 (47)
Ortqvist et al, 1985[7]	53	0 (0)	15 (28)	0 (0)	0 (0)	25 (47)	14 (26)
Present Study, 1992	266	74 (28)	35 (13)	20 (8)	42 (16)	56 (21)	53 (20)

respiratory failure. Mortality in this group was 54% (14/26). In this regard, our experience is similar to that in recent reports discussed earlier and suggests an improving prognosis in HIV-infected patients requiring ICU support because of pneumonia. Changing physicians' attitudes toward earlier and more aggressive ICU support in patients infected with HIV may, in part, explain the improved survival observed in the present analysis. At our institution, patients with HIV infection are encouraged to become active participants in decisions concerning ICU support and mechanical ventilation. Although mortality is increased in patients with pneumonia who have concurrent HIV infection, the expected survival rates are sufficient to warrant providing maximal medical care when so desired by informed patients.

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Articles

Submersion Injuries in Children Younger Than 5 Years in Urban Utah

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Submersion injuries of children younger than 5 years in 4 urban Utah counties from 1984 through 1988 were studied retrospectively to identify associated risk factors. Infants younger than 1 year had the highest rates of both submersion injuries and deaths. The incidence of bathtub drownings was 2 to 3 times higher than reported national rates. All bathtub drownings occurred while the victim was bathing with a young sibling (10 months to 7 years of age) without adult supervision. All drownings in pools and moving bodies of water (rivers, irrigation ditches) resulted from unintentional falls into the water rather than from swimming and wading activities. Drowning prevention strategies should focus on educating parents about the risk of young children bathing with siblings in the absence of adult supervision and fencing regulations for pools and open bodies of moving water.

(Jensen LR, Williams SD, Thurman DJ, Keller PA: Submersion injuries in children younger than 5 years in urban Utah. West J Med 1992 Dec; 157:641-644)

Injuries are the leading cause of death among children older than 9 months in the United States.[1] In many western states, including Utah, submersion injuries, which include both drowning and near-drowning, are one of the most common causes of injury-related deaths in children 14 years of age and younger.[1] Nationally, children younger than 2 years are overrepresented among the victims of submersion injury, accounting for as high as 38% of childhood drownings.[2-4]

Most studies have focused on submersion injuries associated with fatalities, yet submersion injuries also are an important cause of morbidity, with 5% to 20% of survivors left with permanent and severe neurologic sequelae resulting in both ongoing costly medical care and loss of productivity.[5-7] Also, most research has reported submersion injuries in coastal states such as Washington, Florida, and California, but in many noncoastal states submersion injuries are a leading cause of injury death to children.[1]

Previous research has helped identify some of the variables associated with submersion injuries. Bathtubs are the most frequent site of drowning for those younger than 1 year.[2,8,9] Pacific Coast and Rocky Mountain states have the highest mortality from bathtub-related drownings.[10] Swimming pools are the most frequent site of drowning for children 1 to 4 years of age.[2,8,9] In most cases of childhood submersion injury, there has been a lapse in adult supervision.[8]

Understanding the variables associated with childhood submersion injuries is the first step in developing an effective strategy to prevent this pediatric health problem. Our study was conducted to identify the factors associated with submersion injuries along the Wasatch Front, a four-county urban area in Utah. The area has four distinct seasons highlighted by a hot dry summer and a cold snowy winter. There are two major lakes into which the rivers from this area drain, Great Salt Lake and Utah Lake. The hot dry summers and mountain snowpack lead to an extensive system of rivers, irrigation ditches, and canals.

Cases and Methods

We did a retrospective medical records review to profile the circumstances and consequences of submersion injuries of children younger than 5 years from January 1, 1984, to December 31, 1988, in four urbanized counties in Utah—Davis, Salt Lake, Utah, and Weber—home of about 140,000 children during 1986 (the midpoint of our study period), or 77.6% of Utah's pediatric population younger than 5 years. Population data for the period under study were derived from interpolated estimates of the population of the four-county area for 1986 from the 1980 and 1990 US Census.

Cases that occurred in the four-county area during the period of study were obtained from the following sources: death certificates from the Bureau of Vital Records and Health Statistics, Utah Department of Health; records from the Office of the Medical Examiner, Utah Department of Health; and medical records reviews done at local community hospitals and at Primary Children's Medical Center (Salt Lake City), the regional children's hospital.* Hospitals where the medical records were reviewed accounted for 83% of the total pediatric beds and 100% of the pediatric critical care beds in the four-county area. Cases were identified by computerized searches using the International Classification of Disease (ICD) code for drowning or near-drowning (994.1), the ICD-E (external cause) code for submersion (E910.8), or by the cause of death. Records were reviewed for data related to the submersion injury, including outcome,

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site, age, sex, race, date, and presubmersion activity. Cases included only submersion events that occurred within the four-county area and to residents of that same area. Submersion deaths included only those cases where the submersion event and death occurred during the study period.

Results

Outcome

Of the 119 submersion injuries identified during the five-year period, 29 (24%) resulted in death (Table 1). Of the initial 91 survivors, 6 suffered severe neurologic sequelae that resulted in their transfer to an extended care facility. One of these six died during the study period and is therefore included as a submersion death.

TABLE 1.—*Rates of Submersion Injuries, Fatalities, and Case-Fatality by Age for Urban Utah, 1984 to 1988*

Age, years	Injury Rate*	Injury (No.)	Fatality Rate*	Fatality (No.)	Case-Fatality Rate, %
<1	24.2	(33)	6.60	(9)	27
1-4	15.4	(86)	3.58	(20)	23
Total	17.1	(119)	4.17	(29)	24

*Rate is in events/100,000 age-specific population/year.

Age-Specific Rates

The highest rates of injuries, fatalities, and case-fatalities were observed in children younger than 1 year (Table 1). The rates were calculated using age-specific population estimates mentioned earlier.

Of the 119 submersion injuries in this study, 33 (28%) occurred to those younger than 1 year, with all but 1 of these involving infants between 6 and 11 months of age. This older group of infants also accounted for most of both submersion injuries (26/44, or 59%) and deaths (6/8, or 75%) occurring in the bathtub.

Site of Injury Occurrence

Data related to injury site are presented in Table 2. The most frequent site of submersion injury varied with age. The bathtub was the most common site of submersion injury and death for those younger than 1 year. Also in infants younger than 1 year, four submersion events resulting in two deaths involved buckets that had been used for mopping or water storage.

Private pools were the most frequent site of submersion injury for those between the ages of 1 and 4 years. The second most frequent site of submersion injury and the most frequent site of submersion deaths were open bodies of moving water, specifically, rivers, canals, and irrigation ditches.

The case-fatality rate varied with the victim's age and site of injury. The highest rate was observed for events occurring in open bodies of moving water where 11 of 23 (48%) of the injuries resulted in death. For children aged 24 to 35 months, such events resulted in a case-fatality rate of 71% (5/7).

Presubmersion Activity

As expected, the presubmersion activity was site-related. All but one of the bathtub submersion injuries occurred while bathing. In 26 of the 44 bathtub submersion injuries (59%) and in 7 of the 8 bathtub fatalities (88%), the victim was 2 years of age or younger and was bathing with one or more young siblings (ages ranging from 10 months to 7 years) while the parent or babysitter was out of the room. A brief case-by-case description of the above-mentioned injuries is given in Table 3. The other bathtub death involved a 47-month-old boy with a known history of seizures who had a seizure while bathing with a twin in the absence of adult supervision.

Most of the injuries (42/67, or 63%) and all 19 of the deaths that occurred in pools and open, moving bodies of water resulted from unintentional falls into the water rather than during swimming or wading activities. No deaths at any site occurred during a swimming-related activity nor did any deaths occur at public pools.

Race and Ethnicity

The majority of submersion injuries to children younger than 5 years occurred to whites (87%). In those younger than 1 year, however, 21% (7/33) occurred to children of Native American or Hispanic origin. These two ethnic groups represent 6.1% of the total 1990 four-county population.

Season

As expected, the season with the most submersion events was summer. Nearly half (48%) of the events occurred from June 21 to September 21. This seasonal increase was observed even in those younger than 1 year, for whom the most frequent site of submersion injury was the bathtub.

Sex

As expected, male children were involved in more submersion injuries than female children. Overall, there were

TABLE 2.—*Submersion Injuries, Fatalities, and Case-Fatality Rates by Age and Site for Urban Utah, 1984 to 1988*

	Age, years														
	<1					1-4					Total				
	Injury		Fatality		Case-Fatality, %	Injury		Fatality		Case-Fatality, %	Injury		Fatality		Case-Fatality, %
Site	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
Bathtub	26	(79)	6	(67)	23	18	(21)	2	(10)	11	44	(37)	8	(28)	18
Private pool	1	(3)			0	31	(36)	8	(40)	26	32	(27)	8	(28)	25
Moving water	1	(3)	1	(11)	100	22	(26)	10	(50)	45	23	(19)	11	(38)	48
Public pool	--		--		--	12	(14)	--		0	12	(10)	--		0
Lake	--		--		--	2	(2)	--		0	2	(2)	--		0
Bucket	4	(12)	2	(22)	50	1	(1)	--		0	5	(4)	2	(7)	40
Miscellaneous	1	(3)	--		0	--		--			1	(1)	--		0
Total	33		9			86		20			119		29		

TABLE 3.—*Cases of Submersion Injuries Where Victim Was 35 Months Old or Younger and Was Bathing With 1 or More Young Siblings While Parent or Sitter Was Out of the Room*

Case	Age, mo	Sex	Age of Sibling	Supervision	Length of Hospital Stay, days	Comments
1	35	♂	18 mo	Mother	44*	Fell and hit head, witnessed by 7-year-old sibling
2	14	♀	3, 5, 9 yr	Mother	2	Mother called to phone
3	9	♂	2 yr	Mother	1	Empty tub, water running when mother returned
4	20	♂	2½ yr	Father	3†	Father left for "2 to 3 min"
5	9	♀	2 yr	Parents	2†	Mother left assuming father would remain
6	7	♂	20 mo	Mother	1	Left for "5 min"
7	8	♀	4 yr	Mother	2	Phone rang, mother left water running
8	15	♂	3 yr	Mother	3	Found with 3-year-old sibling sitting on patient
9	14	♂	3 yr	Mother	1	Mother left for "1 to 2 min" to answer phone
10	25	♂	4 yr	Father	ED	4-year-old sibling held patient under water
11	12	♀	3 yr	Mother	1	Mother vacuuming
12	10	♀	3 yr	Mother	1	Immersed by older sibling
13	9	♀	2 yr	Father	1	Found in "7 to 8 in" of water
14	11	♀	2 yr	Mother	1†	Mother left to answer phone, found in "4 in" of water
15	10	♀	2 yr	Father	1†	Left for "5 min"
16	10	♂	2, 4, 7 yr	Mother	2†	Found in "7 to 10 in" of water
17	10	♂	10 mo	11-yr-sib	1†	Sister left to get baby bottle, returned to find baby under water, ran to get help before pulling patient out
18	10	♂	2 yr	Father	6†	Found face down in tub
19	24	♂	4 yr	Parents	1	In tub with sib and 3-year-old friend who "pulled patient into tub and submerged his head"
20	11	♂	Preschool	Mother	1	Found face down in tub
21	18	♂	Preschool	Mother	110‡	Mother went to get towel, returned after "1 to 2 min"
22	25	♂	3 yr	Sitter	1	Left for "3 min"
23	8	♂	2½ yr	Mother	1	Found with sibling sitting on patient's head
24	11	♂	11, 26 mo	Mother	1	Mother left for "2 to 3 min"
25	9	♂	9 mo	Mother	ED	In tub with twin, left for "seconds," found cyanotic
26	9	♂	9 mo	Mother	ED	In tub with twin, left for "seconds," found cyanotic

ED = emergency department

*Transferred to an extended-care facility.
†Died.
‡Transferred to an extended-care facility, died 10 months after injury, death occurring after study period.

2.7 injuries to boys for every 1 injury to a girl. The male-to-female ratio was 2.3 for those younger than 1 year and 3.0 for those between the ages of 1 and 4.

Miscellaneous

Other information related to the submersion injury, including socioeconomic status, response time of emergency personnel, length of submersion, the initiation of cardiopulmonary resuscitation, type of fencing for the body of water, water-related experience of the victim, and the suspicion of a nonaccidental injury, was collected. These data are not presented in our results because information available in the records was incomplete.

Discussion

This retrospective study has identified a number of factors associated with drownings and near-drownings among children younger than 5 years in urban Utah from 1984 through 1988. This report is the first to describe submersion injuries occurring at various sites in a noncoastal community. Two high-risk groups emerged from the data: infants or toddlers in bathtubs and preschool-aged children playing near private pools or open bodies of moving water. Although these two groups have distinct risk factors, a common contributing factor is a lapse or absence of supervision.

There is a trend of decreasing drowning rates among children younger than 14 years in the nation[1] and in Utah.[11] The drowning rates obtained in our study for children 1 to 4 years of age are similar to those previously reported.[1,2,5,8,9,11] Yet the drowning rate of 6.6 drownings per 100,000 children per year obtained in our study for children younger than 1 year is two to three times higher than previously reported national rates[1,5] and also somewhat higher than other rates reported from areas in the western United States.[1,2,5,8,9,11] Of note is that most of these infant deaths occur in a bathtub and that children from minority ethnic groups may be overrepresented.

Submersion injury rates are not as well studied as drowning death rates, in part because of inconsistent inclusion criteria for near-drowning victims and in part because of the difficulty in identifying all eligible victims. Definitions of submersion injury victims have varied from all children seen by emergency response personnel to only those who were admitted to a hospital.[5,7,8] Our study included all children younger than 5 years seen in an emergency department, regardless of inpatient admission to the hospital. Our submersion injury rate of 17.1 injuries per 100,000 children per year for children younger than 5 years is considerably less than the estimated national rates of 76.0 injuries per 100,000 children per year for male children younger than 5 years and 44.0 per 100,000 per year for female children under 5 from Wintemute's study in which the definition of submersion injury included all emergency department visits.[5] This estimated national rate was generated by extrapolating regional data

from coastal states (California and Virginia) and may not be representative of the injury rate in a noncoastal area. Yet, the submersion injury rate obtained in our study is greater than that obtained by Quan and co-workers in King County, Washington, where the definition of submersion injury included only those requiring admission to a hospital.[8] They calculated submersion injury rates of 4.0 injuries per 100,000 per year for those younger than 1 year and 12.8 injuries per 100,000 per year for those aged 1 to 4 years.

The association between the lapse of adult supervision of a bathing child and the increased risk of submersion injury is well described.[8] Our study points to another important risk factor, unsupervised bathing with a sibling. All but one of the bathtub-related drownings and the majority (61%) of the injuries occurred in the absence of adult supervision, when a 6-month to 2-year-old child was bathing with a sibling or siblings ranging in age from 2 to 7 years. This likely reflects an overestimation of the sibling's ability to supervise a younger child.

The second risk group identified during this study was toddlers playing near private pools and open bodies of moving water. The association between submersion injuries and private pools is well described,[2,3,5] as is the correlation between pool fencing regulations and a decrease in childhood submersion injuries.[2,5,8,12,13] Bodies of moving water have also been shown to be dangerous, but little has been written regarding fencing regulations for them.[5,8,9] Our study showed that bodies of moving water were the most dangerous site of submersion injury and were especially hazardous for children aged 18 months to 3 years. Reasons for this finding may include the exploring nature of the toddler, the difficulty finding a small victim in moving water, and the distance of these sites from phone contact and medical help.

In Utah, mountain snowpack runoff and irrigated desert farming each result in an extensive system of open bodies of moving water such as streams, irrigation ditches, and canals. Many of these open bodies of moving water are on farmland that has been recently developed into housing subdivisions, which tend to attract young families. This leads to a dangerous scenario: an increased number of young children with possibly inadequate supervision frequently playing near open bodies of moving water.

We recommend that greater emphasis be placed on educating parents that young children should never be left to bathe without adult supervision, even when an older sibling is in the bathtub. Perhaps permanent warning labels should be placed on all bathtubs reminding parents about the danger of leaving children in the tub without adequate supervision in the room. The efficacy of this strategy would need to be evaluated. We also recommend that parents be educated about the dangers of pools and bodies of moving water to preschoolers. A possible way of doing this is through the educational component of the well-child-care visits with a child's primary care provider. Mass education campaigns and stronger fencing regulations for property developers and owners may be more expensive but also more effective.

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Articles

Scombroid Fish Poisoning

Underreporting and Prevention Among Noncommercial Recreational Fishers

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Food-borne diseases, including those caused by seafood products, are common and greatly underreported sources of morbidity. In this article we review the epidemiology of scombroid fish poisoning and its possible relationship to the noncommercial and recreational catch and sale of fish. More than 20% of all fish sold in the United States is caught by sport fishers, and outbreaks of scombroid fish poisoning have involved improperly handled fish from private catches. We report an outbreak of scombroid fish poisoning among recreational fishers in California. The unregulated sale of recreationally caught fish for consumption and the prevention of scombrotoxism are discussed from the perspectives of public health agencies, clinicians, and the fishing public. Scientific and policy issues that require further attention are highlighted.

(Gellert GA, Ralls J, Brown C, Huston J, Merryman R: Scombroid fish poisoning—Underreporting and prevention among noncommercial recreational fishers. West J Med 1992 Dec; 157:645-647)

Food-borne diseases are among the most common and underreported sources of morbidity in the United States. Seafood products are implicated in some of these illnesses. In 1987 US consumption of purchased seafood totaled more than 1.6 billion kg (3.5 billion lb), or 7 kg (15.4 lb) per person per year.[1] An additional 2 kg per person of recreationally caught fish and shellfish was consumed.[1]

Table 1 summarizes several features of naturally occurring seafood toxins and poisons. The highest morbidity worldwide from fish poisoning (ichthyotoxicosis) results from consuming spoiled scombroid fish.[2] The resulting acute illness is called scombroid fish poisoning or scombrotoxism.

Scombroid fish poisoning is a chemical food-borne illness associated with the consumption of improperly handled dark-meated fish from the family Scombridae (yellowfin tuna, skipjack, bonito, mackerel), although outbreaks are also caused by consuming nonscombroid fish (mahimahi, bluefish). The histamine toxin is not contracted from the marine environment, but is produced directly within the flesh of the fish as a result of enteric bacterial action and decomposition (decarboxylation of histidine). This process occurs when fish are not refrigerated properly following capture. Symptoms can appear ten minutes to several hours after the affected fish has been eaten, may last about four hours and resemble a classic histamine reaction with facial flushing, sweating, a burning sensation of mouth and throat, diarrhea, dizziness, nausea, vomiting, abdominal cramps, palpitations, and headaches.[3,4] A metallic, sharp, or peppery taste may be experienced. In severe cases, tachycardia, blurred vision, bronchospasm, and respiratory distress may develop. Despite often dramatic and alarming symptoms, the illness is generally benign and self-limited with no sequelae.[3,4] Treatment has been directed at controlling symptoms.

Epidemiology

Outbreaks of scombroid fish poisoning involving improperly stored fish from private noncommercial or recreational catches have been reported.[3,5,6] Hawaii, New York, and California have the largest number of outbreaks, but 45 states reported outbreaks from 1983 through 1987.[1] Scombroid fish poisoning accounted for 4.5% of all cases of food poisoning reported to the Centers for Disease Control between 1978 and 1982.[7] Between 1973 and 1987, 116 outbreaks (757 cases) of scombroid fish poisoning were reported to the Centers for Disease Control. Of these, 109 (94%) involved mahimahi, tuna, or bluefish.[8] No deaths have been reported.

In most states, sanitary conditions for fish caught and sold are required after the fish enters a seafood or packaging plant. There is generally low risk of seafood-borne disease due to control failures during processing or at the food service level. Because it is caused by bacterial spoilage, scombroid fish poisoning is entirely preventable. Once the toxin is formed, however, no available method of fish preparation, including cooking, freezing, canning, and smoking, will render the fish toxin-free. The most important preventive measure is to ensure that fish are chilled rapidly, then refrigerated adequately and continuously from time of catch to preparation. Fish flesh temperature must be maintained below 15°C.

Reported incidence rates are likely to be considerable underestimates because the illness is generally mild, passes rapidly with no aftereffects, and is therefore not usually reported to health authorities. Scombroid fish poisoning is probably much underreported and misdiagnosed as "fish allergy" because scombrotoxism is symptomatically similar to an allergic response. Seafood intolerance, however, is rare. Food-borne diseases are generally acknowledged to be heavily underreported, and because fish has become an increasingly important part of the American diet in recent decades, it follows that the incidence of scombroid fish poisoning is similarly underestimated.

Noncommercial and Recreational Catch and Sale of Fish

The commercial fishing industry is responsible for few incidents of scombroid fish poisoning, and industry controls

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TABLE 1.—*Characteristics of Toxins and Poisons That Occur Naturally in Seafood*

Type of Toxin or Poison	*Seafood Involved*	*Cause*	*Signs and Symptoms*	*Onset*	*Duration*	*Treatment*
Scombroid fish poisoning	Mahimahi, tuna, bluefish, mackerel, skipjack	Histidine in flesh decarboxylated by action of *Proteus* species or other bacteria	Metallic or peppery taste; intense headache, dizziness, nausea, vomiting, facial swelling and flushing, throbbing of carotid and temporal vessels, rapid and weak pulse, burning of throat, itching of skin; generalized erythema and urticarial eruptions	Few minutes to 4 hr	Up to 24 hr	Administering antihistamines results in immediate improvement of condition
Ciguatera poisoning	Tends to be fish from coral reefs (>400 species)	Ciguatoxin; lipid-soluble, polyether multicomponent	Abdominal pain, diarrhea, vomiting, paresthesia, vertigo, ataxia, cold-to-hot sensory reversal, myalgia, itching	3 to 5 hr, up to 24 hr	24 hr usually, but neurologic effects up to 6 mo	No effective antidote; mannitol may be effective in acute cases
Paralytic shellfish poisoning	Mussels, clams, other shellfish; some finfish	Saxitoxin or related compounds; purine base, water soluble	Tingling or burning and numbness around lips and fingertips; respiratory paralysis within 12 hr; patients often report feeling of lightness or floating on air	<1 hr	Prognosis good after 24 hr	No antidote; artificial respiration, rest
Neurotoxic shellfish poisoning	Bivalves and most plankton feeders	Neurotoxin from *Ptychodiscus*; lipid-soluble polyether	Similar to mild case of ciguatera or paralytic shellfish poisoning	<3 hr	<48 hr	No specific treatment
Amnesic shellfish poisoning	Mussels, clams, crabs, anchovies	Domoic acid	Vomiting, cramps, diarrhea, short-term memory loss, disorientation, facial grimace or chewing motion; memory loss can be long term and in severe cases can cause brain damage or death	24 to 48 hr	Unknown	No known antidote

for detection are in place. More than 20% of all fish sold in the United States is caught by sport fishers,[1] and several outbreaks of scombroid fish poisoning have involved improperly handled fish from private catches. No federal or state regulatory agency makes physical examinations of the fish, equipment, or storage conditions on recreational boats. In most states, the fish and game department issues commercial and sport fishing permits. For a higher licensing fee, sport fishers can sell their catches. Fish may pass from noncommercial and recreational boats directly to markets, restaurants, and distributors without being subject to the regulations imposed on the commercial fishing industry (such as inspections or controls before distribution or wholesale and retail sales). Therefore, sport-caught fish present a control problem because they are caught by fishers who either do not enter commercial channels or do so in an unconventional manner.[1]

Recreational boats that lack adequate refrigeration capability may be chartered by sport fishers. Fish flesh temperatures on such vessels can easily exceed 20°C, and it is not uncommon for fish to be held on deck at even higher temperatures for several hours. Histamine, the causative biochemical agent of the illness, is optimally produced at 30°C. Once a large population of bacteria has been established, residual enzyme activity continues slowly at refrigeration temperatures (0°C to 5°C) even though bacterial growth ceases. Rinsing fish in seawater during handling and cleaning, or for cooling, may contribute to the problem because many of the microorganisms capable of metabolizing elements of fish flesh to histamine are found in the marine environment. Rapid, reliable tests for scombrotoxin are not available.

Report of an Outbreak of Scombroid Fish Poisoning Among Recreational Fishers

An outbreak of scombroid fish poisoning occurred among eight persons who had consumed fish caught off the coast of southern California by a recreational fisher in October 1990. Two species of fish were involved, yellowfin and skipjack tuna, with no other foods eaten during the implicated meal. The fish had no foul odor and showed no "honeycombing" of surfaces.

Because only yellowfish and skipjack tuna were eaten at the meal, no food-specific attack rates can be calculated. The age range of afflicted persons was 21 to 45 years, with a mean of 33 years. The mean incubation time between the ingestion of fish and the onset of clinical symptoms was 71 minutes. Of seven persons from whom a history of symptoms was obtained, all had diarrhea, all had headache, four vomited, four had skin flushing or rash, three had dizziness, and two had peculiar oral sensations. No urticaria, pruritus, or bronchospasm was noted. One person sought medical attention.

The vessel had been rented commercially at a local dock. The fish were caught at 6 AM by one of the eight people involved on a vessel that had no onboard facilities for refrigerating the catch. The fish were cleaned at about 3:30 PM; the vessel did not dock until 10 PM. The catch was eventually smoked. Six fish specimens were tested for histamine levels. The histamine levels in the specimens ranged from 607 to 840 mg per 100 grams (mean 696 mg, median 667 mg). Because the fish were already smoked when received by the laboratory, it was not possible to differentiate histamine levels by the type of fish.

According to the Food and Drug Administration, accept-

able histamine levels are not to exceed 20 mg per 100 grams, with a hazard action level in tuna defined as 50 mg per 100 grams (fresh fish contains less than 1 mg per 100 grams of histamine).[9] The histamine levels identified in fish from this vessel are among the highest recorded in the literature for fish samples obtained in an outbreak setting. Most investigators have reported levels ranging from 10 mg to 250 mg per 100 grams; the highest level reported was 821 mg per 100 grams.[10]

The fisher in this incident appeared to be unaware of the potential problems associated with improper refrigeration of scombroid fish. In addition, because these fish were smoked, the persons may have had a false sense of assurance against ill effects from decomposition.

Prevention of Scombrotoxism

Recreational and subsistence fishers are at risk for scombrotoxism. The food service industry, the public, and health professionals have little understanding of the infrequent but distinct hazards present in seafood. Scombroid fish poisoning is probably highly underreported, and surveillance capabilities must be improved. Disease control will depend on educating sport fishers, especially about the importance of assessing the refrigeration capability of sporting boats as a criterion for chartering a vessel.[11] The outbreak reported here is an example of the risk engendered by recreational fishers among those to whom they provide a fish catch.

Inspection based on human sensory perception, such as fish appearance and odor, is of no value in detecting and controlling health risks. State health agencies can assume an active role in educating sport fishers on disease prevention. States should provide advisory bulletins on scombrotoxism as an integral component of the licensing process for recreational fishers. Local health agencies should post educational messages about the need for adequate refrigeration at docks and other locations where vessels are chartered, along with information on how to report occurrences of scombroid fish poisoning. If surveillance confirms substantial underreporting, the incidence of scombrotoxic disease may warrant a regulatory role for local health agencies in ensuring that chartered vessels have adequate refrigeration capability to engage in commercial recreational fishing.

Remaining Scientific and Policy Issues

Several basic scientific and policy issues should be addressed with respect to scombroid fish poisoning. Important questions concern what are accurate incidence estimates of scombrotoxic disease and how best to model estimates. Levels of surveillance must be increased. A recent report of the National Academy of Science, Institute of Medicine, recognized the need for an improved national surveillance system to provide more reliable and comprehensive information on the incidence of seafood-borne disease.[1]

To reduce confusion, we need to better assess the actual incidence of fish allergy and determine what percentage of cases diagnosed as fish allergy represent misdiagnosis and misclassification of scombroid fish poisoning. The symptoms of the two conditions may overlap because both share a rapid onset and transience, and both may cause such symptoms as vomiting, headache, and nausea. The biochemical and immunologic characteristics of seafood allergies should be investigated further to achieve this objective. Scombroid fish poisoning may be differentiated from allergy by the occurrence of clusters of affected persons. A history of several cases of illness resulting from a common meal, as well as identifying the specific species of fish as one typically associated with scombroid fish poisoning, should raise the suspicion of scombrotoxism.

Public health practitioners need to identify the prospective regulatory roles and potential of state and local health departments in helping prevent scombroid fish poisoning. Intergovernmental responsibilities and roles in public education and regulation should be clearly delineated. The possibility of an interjurisdictional regulatory collaboration among selected coastal cities and counties should be explored. Determining what data are available on the number and annual catch weight of recreational fishing vessels for charter will help to direct regulatory activities.

The knowledge level of recreational fishers on this public health problem must be heightened. In view of the recent confirmation of histamine as the causative agent of scombrotoxism,[12] physicians and the public should be educated on the use of antihistamines in clinical and self-treatment. This breakthrough in comprehending the basic pathogenesis of scombroid fish poisoning should not, however, obscure the inherent public health nature of this problem and of the most effective control measures.[11] To recommend that physicians counsel patients who fish about the need to chill their catch rapidly and to maintain refrigeration until the fish is prepared for eating is an incomplete solution to this problem.[13] State and local health agencies, not clinicians, have the primary responsibility for addressing the prevention of food-borne disease. Maintaining the temperature of fish flesh below 15°C should become routine practice in all types of fishing. Physicians most frequently manage illness when such prevention efforts fail. Health providers nonetheless should be educated on the identification and treatment of scombroid fish poisoning so that they can conduct office-based preventive education among their clients who are known to be sport fishers.

Finally, from the environmental health perspective, it is imperative that a rapid assay for detecting scombrotoxin be developed for use in subsequent regulatory activities. If inexpensive and relatively simple, such rapid assays could be made available to the public and, in particular, to recreational fishers.

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Articles

Seizures After Eating a Snack Food Contaminated With the Pesticide Endrin

The Tale of the Toxic Taquitos

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In September 1988 we investigated reports of seizures in persons who had eaten taquitos, a commercially prepared snack food. We identified and interviewed 5 persons with new-onset seizures within 12 hours of eating taquitos, all purchased during a 1-week period from a single store. Leftover taquitos were found to contain endrin, a highly toxic chlorinated hydrocarbon pesticide. Although tissue confirmation of exposure to endrin was not possible and the level of contamination in the tested taquitos was below that previously thought to be capable of inducing seizures, the pattern of symptoms and the common time and place of purchase strongly suggested that the seizures were due to endrin-contaminated taquitos. The source of endrin contamination could not be determined. This episode is the first report of illness associated with endrin-contaminated food products in the United States.

(Waller K, Prendergast TJ, Slagle A, Jackson RJ: Seizures after eating a snack food contaminated with the pesticide endrin—The tale of the toxic taquitos. West J Med 1992 Dec; 157:648-651)

Pesticides are widely used on food crops in the United States; in 1988, 76.7 million tons of pesticides were used in California alone.[1] Pest-control products are also extensively used in establishments that process, sell, and serve food. Despite the potential for contamination, published reports of acute illness due to food-borne pesticides in this country are relatively rare.[2-5] This may be due in part to the nonspecific nature of many symptoms of pesticide poisoning, difficulty in confirming pesticide exposure, and a low index of suspicion on the part of physicians. In this report we describe an investigation of seizures after the ingestion of a commercially prepared snack food that was found to be contaminated with the pesticide endrin.

Background

On March 15 and 16, 1988, two members of a southern Orange County family (the index family) suffered multiple generalized seizures within an hour of eating taquitos, a snack food consisting of a corn tortilla wrapped around a meat filling. The product, sold frozen in sealed plastic bags containing 48 taquitos, had been recently purchased from a warehouse-style discount store. The attending physician suspected a toxic exposure and reported the cases to the county health department; the store stopped selling taquitos the next day.

Six of the family's taquitos were sent to the United States Department of Agriculture, where they were tested for organochlorine and organophosphate pesticide residues. The taquitos were found to be contaminated with endrin, a chlorinated hydrocarbon pesticide, in a concentration of 100 parts per million (ppm) in the extracted fat. Because the taquitos were pooled for the analysis and as the percentage of fat content was not recorded, the concentration of endrin per taquito could not be calculated nor could it be determined if the pesticide was concentrated in one taquito or distributed among several. Taquitos from two comparison bags taken from the discount store tested negative for pesticide residues. After interviewing the family, their physicians, and the manufacturer, the US Department of Agriculture judged the episode to be an "isolated incident" and closed the case in April.

In September 1988 the county health department was notified of a third person who on March 15 had also had seizures after eating taquitos. All three case-patients had eaten the same brand of taquitos purchased from the same store. In light of this information, county and state health officials began a new investigation. The objectives were to determine if others had had seizures soon after eating taquitos; to evaluate the likelihood that the seizures were caused by endrin poisoning; to find the source of endrin contamination; and, if necessary, to initiate measures for consumer protection.

Methods

Case Investigation

A case of taquito-associated seizures was defined as an unexplained new occurrence of seizure—that is, no evidence of trauma; an intracranial mass, hemorrhage, or infection; alcohol withdrawal; or other structural or metabolic abnormality that could cause a seizure—that occurred in a person within 12 hours of eating taquitos. Cases were ascertained by the following methods:

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TABLE 1.—*Case Characteristics of Persons With Taquito-Associated Seizures, 1988*

Case	Age, years	Weight, kg	Date Purchased, March 1988	Month/Day of Illness Onset	Taquitos Eaten, No.	Nausea	Time to Onset of Dizziness*	Time to Onset of Seizures*	Seizures, No.	Comments
1†	11	38.6	13	3/15	4	Yes	30 min	50 min	2	Respiratory arrest
2†	38	95.5	13	3/16	4	Yes	30 min	45 min	2	Stepfather of patient 1
3	16	81.8	13	3/15	10-14	Yes	20-30 min	30-40 min	4	--
4	17	75.0	13-17‡	3/22	6-7	Yes	2 hr	4-5 hr	1	Myoclonus preceded seizure
5	19	63.6	17‡	7/23	5-6	No§	1-2 hr	5-6 hr	1	Taquitos stored in garage freezer

*Time refers to from the ingestion of taquitos.
†These were the index cases.
‡These patients reported that it was likely, but not certain, that the taquitos purchased at this time were the taquitos eaten before the onset of seizures.
§Patient 5 had postseizure nausea only

• The management of the discount store mailed a letter to 40,500 recent customers of the implicated store and nearby stores belonging to the same chain. The letter explained that some consumers had become ill after eating contaminated taquitos and requested that persons who either had experienced symptoms or had taquitos left in their freezers (or both) contact the county health department. The county kept a log of all responses to the letter, detailing the place and time of purchase, symptoms experienced, and their date of occurrence.

• Southern Orange County Emergency Medical Service system records were reviewed to identify persons transported for suspected seizures from January through April 1988. If hospital records confirmed a diagnosis of unexplained new-onset seizures, we attempted to contact the person by telephone and administer a standardized questionnaire regarding food intake in the 24 hours before their illness.

• A description of the incident was sent to all neurologists belonging to the medical societies of Orange County and two adjacent counties. Reports of additional possible cases were requested.

We interviewed symptomatic persons by telephone, ascertaining their medical history, dates of taquito purchase, symptoms, details of medical evaluation and treatment, foods consumed before illness, and the status of other persons in their family who also ate taquitos. One of us (K.W.) reviewed the hospital records of all persons meeting the case definition.

Laboratory Investigation

Three remaining taquitos from the index family and taquitos from five other families who had purchased the product during March 1988 were analyzed by California Department of Food and Agriculture laboratories in September 1988. Gas-liquid chromatography and mass spectrometry were used to determine concentrations of endrin; the minimum detection limit was 0.05 ppm. Both blank and spiked specimens were analyzed to assure the quality of measurements. Tortilla shells and meat fillings were analyzed separately.

Product Investigation

Investigators from the California Department of Health Services Food and Drug Branch conducted environmental inspections of the store, the taquito manufacturing plant, and the cornmeal distributor. This included observing production and storage methods, reviewing ingredient sources, and searching the premises for pesticide-containing products.

Results

Case Investigation

In addition to the three previously identified cases, two additional cases were found through the mass mailing to store customers; thus, a total of five persons who met the case definition were identified. Interviews with ten seizure patients transported by ambulance and the mailing to neurologists failed to identify any more cases.

All five cases were in males, and three were in teenagers (Table 1). All case-families reported purchasing taquitos from the same store during a five-day period in mid-March. Two families had purchased the product on numerous occasions, however, and could not be certain that these were the taquitos associated with illness. Four of the patients experienced seizures in March 1988; the fifth became ill in July after eating taquitos that had been stored unopened for several months in a freezer. Other than taquitos, there were no foods commonly consumed among the five patients.

The presentation of illness was strikingly similar among the cases. All five patients had been previously healthy, with no personal or family history of convulsions. All felt dizzy within two hours of eating the taquitos; four also reported nausea. Generalized seizures began 30 minutes to 6 hours after taquito ingestion. Three patients had at least two seizures before regaining consciousness; all patients vomited after their seizures.

Case-patients 1 through 4 received medical evaluations immediately after their seizures, including computed tomography of the head, routine blood toxicology screens for prescription and illicit drugs (including cocaine), and/or electroencephalograms; the fifth patient refused medical treatment. These tests failed to identify a cause for the seizures in all instances. A toxic cause was suspected in only the two index cases; a food history was recorded in the medical records of only one case. No blood or tissue specimens were saved from any of the case-patients. To date, none of the case-patients have had recurrent seizures.

In each of the families, others had eaten taquitos without seizures developing. Of ten persons who had eaten from suspect bags, five of six who ate four or more taquitos at a time had seizures develop, whereas none of those who usually ate less than four had seizures ($P=.05$, Fisher's exact test).

Laboratory Investigation

Each tortilla shell of the index family's taquitos was found to be contaminated with endrin in concentrations ranging from 2.4 to 4.6 ppm (Table 2). No endrin was found in the

meat filling in any of the taquitos. The estimated amount of endrin per taquito ranged from 44 to 84 μg. The families of patients 3 to 5 had no taquitos available for testing. Five other families, on receiving the mass mailing, provided bags of taquitos that had been purchased in March 1988. All these taquitos were negative for pesticide residues.

Product Investigation

Inspections of the store, manufacturing plant, and cornmeal distributor failed to identify a source of endrin contamination. All tortilla ingredients reportedly came from within the United States. The retail store reported that 211 bags of taquitos had been sold from March 13 to 17, 1988.

Discussion

Endrin, the most toxic member of the organochlorine family of pesticides, has been responsible for more than 1,100 reported cases of illness and 45 deaths in outbreaks of food-borne poisoning in Wales,[6] Qatar and Saudi Arabia,[7] Egypt,[8] and Pakistan[9,10] (Table 3). As with related pesticides (such as DDT [dichlorodiphenyltrichloroethane] and dieldrin), symptoms of endrin poisoning are primarily due to central nervous system excitation and include severe dizziness, leg weakness, tremors, confusion, belligerence, and generalized seizures. Other symptoms include nausea, abdominal pain, and vomiting. Symptoms occur within 12 hours after ingestion; at higher doses, seizures may occur without premonitory symptoms.[11] Because of concerns regarding its toxicity to humans and wildlife, endrin has been banned from agricultural use in the United States since 1984.[12] At the time of this investigation, the only legal use for endrin was in a nuisance-bird control device. The use of the device is strictly controlled, and, according to the manufacturer, it has not been used in California.

TABLE 2.—*Concentration of Endrin and Dose Calculations in Index Family's Taquitos, California Department of Food and Agriculture Laboratories, September 1988*

Taquito	Endrin in Tortilla, ppm	Endrin in Filling*	Dose/Taquito, μg†
1	4.0	ND	73
2	2.4	ND	44
3	4.6	ND	84

ND = none detected

*Minimum detection level = 0.05 ppm.

†Dose is calculated using the following formula: (endrin in ppm/tortilla) × (18.3 grams tortilla/taquito).

At the time of our investigation (6 months after the seizures occurred), only one case-family still had taquitos available for testing. No blood or tissue specimens had been saved from any of the patients. In addition, the short half-life of endrin in humans (1 to 3 days)[13-17] meant that current examination of patients' blood or tissue for evidence of endrin exposure would not be useful.

Despite these obstacles, available evidence points to endrin as the cause of the patients' seizures. The finding that all patients had eaten taquitos purchased from a single store during a limited period of time suggests a common cause. Endrin was found in the index family's taquitos; other pesticides capable of causing similar symptoms were not found. Furthermore, features of the patients' clinical presentations, in particular dizziness, gastrointestinal symptoms, and multiple seizures, are somewhat unusual for new-onset idiopathic seizures,[18] but are consistent with endrin toxicity. Finally, it is unlikely that the taquito-associated case-patients represented a random aggregation of persons with newly occurring seizures. A total of 211 bags of taquitos were purchased from March 13 to 17, 1988. If an average of five persons ate from each bag, 1,055 persons consumed these taquitos. In a group of this size, about 0.8 cases of new-onset afebrile seizures over the course of a year would be expected[19] compared with the five cases observed ($P = .0014$, exact Poisson probability).

Although these points argue that endrin was the probable cause of the seizures, the level of contamination in the tested taquitos was below that previously thought to be capable of inducing seizures. In 1963 Hayes estimated that an endrin dose of 0.2 mg per kg of body weight was needed to produce convulsions in humans.[16] Extrapolating from the California Department of Food and Agriculture measurements, the smallest patient (case 1) would have had to consume 92 taquitos to reach this threshold. It is possible that the taquitos eaten by the patients were more contaminated than others in the bag or that illness occurred only in persons susceptible to lower doses of endrin. Alternatively, the "seizure threshold" for endrin may be lower than previously thought.

We were unsuccessful in discovering the source of the endrin contamination. Possibilities include the use of endrin on the grain used to make the cornmeal, contamination of vehicles or containers used to transport tortilla ingredients, or deliberate or inadvertent contamination after the taquitos were manufactured.

The episode described here is, to our knowledge, the first report of illness associated with endrin-contaminated food products in the United States. Although episodes of acute toxicity due to food-borne pesticide contamination are probably rare, a finding of pesticide-related illness from a com-

TABLE 3.—*Summary of Previously Reported Outbreaks of Illness Due to Eating Endrin-Contaminated Food*

Location	Ill Persons, No.	Deaths, No.	Implicated Food	Level of Endrin Contamination, ppm (source)	Mechanism of Contamination
Wales*	59	0	Flour	200-5,500 (flour) 150 (bread)	Flour sacks absorbed spilled endrin on floor of railcar
Qatar, Saudi Arabia†	874	26	Flour	153-3,367 (flour) 48-1,807 (bread)	Endrin containers leaked onto flour during ship transport
Egypt‡	3	0	Flour	126-176 (bread)	Not known
Pakistan§‖	194	19	?Sugar (not confirmed)	0.04 (pooled sugar sample)	Not known

*From Davies and Lewis.[6] †From Weeks.[7] ‡From Coble et al.[8] §From Centers for Disease Control.[9] ‖From Rowley et al.[10]

mercial product should prompt a rapid and thorough investigation to identify additional cases and the sources of contamination. Clinicians should be alert to possible pesticide exposures when evaluating patients with newly occurring seizures, even among persons without occupational exposures. Directed questioning regarding pesticide exposures and recent food intake or additional toxicologic testing may uncover diagnostic leads. Specimens of blood and the possibly contaminated food items should be saved until the investigation is complete. Physicians who suspect the possibility of food contamination are urged to contact their local health department and the US Food and Drug Administration. In California, physicians can contact the Food and Drug Branch of the Department of Health Services (916-445-2263).

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Conferences and Reviews

Orthostatic Hypotension
Causes, Evaluation, and Management

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Chronic orthostatic hypotension is caused by a variety of disorders. Frequently patients withdraw from social interactions, are prone to adverse drug reactions and inappropriate diagnoses, and are bed-bound by the time of diagnosis. Applying basic principles of cardiovascular physiology and pharmacology usually permits these patients to lead active lives and to live longer. Much of the management is based on common sense and knowledge of the basic pathophysiology of the disorder and depends on thorough patient education and close monitoring of blood pressure in many of the activities of daily living.

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Orthostatic hypotension may be defined as any postural fall in blood pressure that results in symptoms referable to cerebral hypoperfusion. This definition purposefully avoids absolute values for blood pressure because a wide range of cerebral perfusion pressures may be tolerated by individual patients. The prevalence of chronic orthostatic hypotension in the general population has been estimated at 5 per 1,000,[1] but the incidence of orthostasis in acute medical care settings ranges from 7% to 17% of all patient contacts.[2,3]

Causes of Orthostatic Hypotension

A wide variety of medical conditions may primarily or secondarily cause orthostatic hypotension. These may be broadly categorized as reduced effective blood volume, drug-induced hypotension, miscellaneous disorders, and autonomic disorders.[1,4-6]

Reduced effective blood volume may result from various conditions. Acute and subacute intravascular volume losses due to hemorrhage, burns, sepsis, dialysis, excessive diuresis or sweating, hyperglycemia, and diabetes insipidus are readily apparent causes of orthostasis, accompanied by pronounced tachycardia. Intravascular volume contraction occurs frequently in pheochromocytoma, Addison's disease, vipomas, chronic diarrheal illnesses (especially cholera), renovascular hypertension, salt-losing nephropathy, and anorexia nervosa. A relative insufficiency of intravascular volume is present in large venous varicosities, left-to-right shunts, arteriovenous malformations, absence of venous valves, the last trimester of pregnancy, hyperthyroidism, beriberi, and probably mitral valve prolapse. Paroxysmal hypovolemia may be caused by the dumping syndrome, hyperosmolar feedings (particularly following gastrectomy), hypermagnesemia, and the release of excessive amounts of vasodilators in carcinoid syndrome, mastocytosis, and hyperbradykininism.

The drugs most commonly causing symptomatic orthostatic hypotension are listed in Table 1. Miscellaneous causes of orthostatic hypotension include cardiac dysrhythmias, angina, heart failure, pulmonary embolism, atrial myxoma, hypokalemia, paraneoplastic syndromes, and the sympathetic deconditioning that occurs with prolonged bed rest or weightlessness.

Autonomic Disorders Causing Orthostatic Hypotension

The major neurogenic causes of orthostatic hypotension are the Shy-Drager syndrome,[7] idiopathic orthostatic hypotension,[8] peripheral neuropathies, and parasympathetic reflex activation. Lesions and surgical procedures in the posterior fossa and upper cervical spinal cord may interrupt the autonomic control of blood pressure or heart rate or both, resulting in orthostatic hypotension. Other causes may include hydrocephalus, medullary plate syndromes, Wernicke's encephalopathy, multiple cerebral infarcts, multiple sclerosis, craniopharyngioma, and syringomyelia. Major neurologic defects associated with orthostatic hypotension—the Shy-Drager syndrome or multiple system atrophy—include Parkinson's disease, pseudobulbar palsy, cerebellar degeneration, and olivopontocerebellar atrophy. Familial dysautonomia—the Riley-Day syndrome—is an inherited disorder with widespread neurologic deficits and autonomic dysfunction.[9] Recently, encephalopathy due to the acquired immunodeficiency syndrome has been associated with orthostatic hypotension and multiple neurologic deficits.[10,11] Each of these central nervous system causes of orthostatic hypotension may be viewed as a disconnection of the central

TABLE 1.—*Drugs Cousing Orthostatic Hypotension*

Tricyclic antidepressants	Alcohol
Sympatholytics	Narcotic agents
Vasodilators	Vincristine sulfate
Diuretics	Perhexiline
Phenothiazine derivatives	Sympathomimetic agents (prolonged use)
Minor tranquilizers	Marijuana
Nitrates	
Insulin	

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integrative control of blood pressure from the peripheral autonomic nervous system.

Idiopathic orthostatic hypotension—the Bradbury-Eggleston syndrome—is caused by a progressive loss of the peripheral preganglionic and postganglionic autonomic nerves for reasons that have not yet been elucidated. Sympathicotonia, a poorly defined and poorly understood syndrome associated with orthostatic tachycardia, malaise, and psychiatric disturbances, also has been called neurasthenia, the effort syndrome, soldier's heart, somasthenia, DaCosta's syndrome, neurocirculatory asthenia, and hyperadrenergic syndrome.[12-15] From the 1940s through the early 1960s, lumbar sympathectomies were occasionally used to treat uncontrollable hypertension and resulted in marked orthostatic hypotension.[16] Baroreceptor dysfunction caused by irradiation, surgical treatment, tumor, or glossopharyngeal neuralgia may result in paroxysmal orthostatic hypotension, a blood pressure that is directly dependent on the heart rate, or both.[17] The activation of parasympathetic reflexes—with and without sympathetic withdrawal—by hollow viscus distension, increased intraocular pressure, carotid sinus pressure, swallow, hiccup and cough, vasovagal reactions (including the Bezold-Jarisch reflex), myocardial ischemia, and micturition all result in paroxysmal falls in blood pressure.[6,18] Dopamine-β-hydroxylase deficiency has been described as a cause of profound orthostatic hypotension coupled with an absence of norepinephrine synthesis.[19]

Many forms of peripheral sensory and motor neuropathy may also involve the autonomic nervous system and result in orthostasis (Table 2). Of the causes listed, amyloidosis most frequently is accompanied by isolated autonomic insufficiency, but patients with Guillain-Barré and paraneoplastic (Eaton-Lambert) syndromes, porphyria, and occasionally alcoholism may present initially with autonomic neuropathy.

TABLE 2.—*Causes of Peripheral Neuropathy That May Result in Orthostatic Hypotension*

Diabetes mellitus	Renal failure
Alcoholism	Recurrent peripheral neuropathy
Nutritional deficiency: vitamin B_{12}, folate	Amyloidosis
Guillain-Barré syndrome	Porphyria
Toxins, drugs	Infectious agents: diphtheria, tetanus, botulism
Heavy metals	Systemic collagen vascular diseases
Hereditary	Syringomyelia
Hansen's disease	Tabes dorsalis
Paraneoplastic (Eaton-Lambert) syndrome	

Specific Syndromes Causing Chronic Orthostatic Hypotension

Diabetes Mellitus

Diabetes mellitus is the most common cause of autonomic neuropathy but rarely results in disabling orthostatic hypotension.[20] Autonomic neuropathy usually manifests as gastrointestinal problems of chronic diarrhea and gastroparesis, but an early loss of sinus arrhythmia and decreased sweating also occur. Orthostasis may develop many years after the onset of peripheral sensory and motor neuropathy because of a loss of postganglionic nerves. A failure of venous vasoconstriction in the lower extremities and splanchnic vascular beds, reduced basal and posture-stimulated plasma norepinephrine levels, and a reduced renin response to posture have all been demonstrated in diabetic patients and contribute to the orthostasis. Insulin therapy may further complicate orthostatic hypotension in these patients because it decreases plasma volume, causes vasodilation, and increases heart rate.

Idiopathic Orthostatic Hypotension (Bradbury-Eggleston Syndrome)

The Bradbury-Eggleston syndrome is an idiopathic degeneration of the peripheral autonomic nervous system that presents late in life and afflicts men four to five times more often than women. The onset of the disease is insidious, occurring over two to five or more years.

Impotence, sphincter disturbances, and postprandial syncope are the most common presenting symptoms of patients with this syndrome, but orthostasis and supine hypertension also are common diagnostic clues. Many patients withdraw from social contact because of embarrassing episodes of syncope or near-syncope, an inability to drive at night, intolerance to heat, and urinary incontinence. Patients may give a history of treatment of hypertension with intolerance to medications; previous episodes of urinary tract obstruction, occasionally treated with transurethral resections of the prostate; cardiac catheterizations for angina in which normal coronary arteries and excellent ejection fractions were found; treatment of allergies, transient ischemic attacks, or seizures; and many urinary tract infections. Characteristically, episodes of syncope or near-syncope are not accompanied by sweating, nausea, pallor, shortness of breath, or tachycardia.[6,21,22]

Although the cause of the loss of preganglionic and postganglionic autonomic neurons is not known, the consequences of this loss are well documented. Plasma levels of norepinephrine are reduced, usually below 0.59 nmol per liter (100 pg per ml), as are urinary levels of all three catecholamines. There is a loss of cell bodies in the intermediolateral column of the spinal cord and a loss of catecholamine fluorescence in sympathetic ganglia and target organs. A substantially reduced or absent catecholamine response is seen to an upright posture and insulin-induced hypoglycemia, and there is virtually no rise in renin, angiotensin II, or aldosterone levels with an upright posture. These patients are extremely sensitive to α- and β-adrenergic agonists,[23,24] and strokes have occurred after normal doses of over-the-counter cold preparations. No cognitive dysfunction or central neurologic deficits are associated with the Bradbury-Eggleston syndrome, and most patients have a life expectancy of more than ten years, despite their advanced age at diagnosis.

Shy-Drager Syndrome (Multiple System Atrophy)

This disorder usually presents in mid- to late life as orthostatic hypotension associated with major neurologic deficits referable to the corticobulbar, corticospinal, extrapyramidal, and cerebellar systems. Lower motor neuron lesions are occasionally present as well. No sensory or cognitive impairments are present, and the peripheral autonomic nervous system appears to be intact but disconnected from the central nervous system. Cell bodies are present in the intermediolateral column of the spinal cord and in the sympathetic ganglia, and peripheral sympathetic nerve catecholamine

content and fluorescence are normal. Plasma and urine catecholamine concentrations are in the normal range and are releasable by indirect-acting sympathomimetic drugs, but do not change with an upright posture.[5]

Patients with the Shy-Drager syndrome exhibit slowly progressive deterioration, with increasing neurologic deficits, periodic respirations, difficulty swallowing, and laryngeal stridor as ominous signs. Respiratory arrest and pulmonary embolus are frequent causes of death, occurring an average of seven to eight years after the first manifestations of disease. Occasionally orthostatic hypotension will precede the onset of focal central neurologic deficits and prompt an initial misdiagnosis of the Bradbury-Eggleston syndrome.

Riley-Day Syndrome (Familial Dysautonomia)

The Riley-Day syndrome is an autosomal recessive neuropathy that affects about 1 in 5,000 Ashkenazi Jews. It is usually identified at birth or shortly thereafter by the presence of widespread neurologic deficits, including areflexia or hyporeflexia, poor motor coordination, mental retardation, a relative indifference to pain, emotional lability, and orthostatic hypotension.[9] The patient's body temperature varies widely, there is increased sweating and decreased tearing, and pulmonary infections are frequent. Infant mortality for patients with this disorder is high, but enough patients survive to adulthood to yield an average life expectancy of 22 years.

Baroreceptor Dysfunction

Baroreceptor dysfunction usually occurs late in life and is often associated with neck irradiation, trauma, surgery, or a local spread of oropharyngeal carcinoma. It is manifested by wide variations in blood pressure that are dependent on the heart rate.[23] Many patients with baroreceptor dysfunction have periods of supine and upright hypertension and receive antihypertensive medications with uniformly adverse consequences. Similarly, administering sedatives may result in dramatic falls in blood pressure. Glossopharyngeal neuralgia is a paroxysmal form of this disorder, presenting as pain in the side of the neck or jaw followed within a minute by sympathetic withdrawal and parasympathetic activation. This results in hypotension and bradycardia, which may be fatal.[17] Glossopharyngeal neuralgia is usually caused by irritative lesions of the carotid sinus nerve, but occasionally no inciting cause has been found. The successful treatment of cancer-associated baroreceptor dysfunction has usually involved the intracranial section of the caudal rootlets of the ninth and the rostral rootlets of the tenth cranial nerves.[25,26] Chronic baroreceptor dysfunction has been managed with a combination of cardiac pacemakers plus β-adrenergic blocking agents.

Dopamine-β-Hydroxylase Deficiency

Eight patients have been found to have a deficiency in dopamine-β-hydroxylase, resulting in severe orthostatic hypotension. In retrospect the disease is manifested shortly after birth, but frequently it is misdiagnosed as seizures, sudden infant death syndrome, hypoglycemia, and hypothermia. Mothers of these infants have a high incidence of spontaneous abortions and stillbirths. Cognitive function in these patients is normal. The most common clinical features of the six patients diagnosed by us are shown in Table 3.[27]

Plasma, urinary, and spinal fluid concentrations of norepinephrine and epinephrine are below detectable limits in patients with this condition, and plasma dopamine levels are greatly increased. All sympathetically mediated cardiovascular reflexes are greatly diminished, but sinus arrhythmia, increased heart rate after the administration of atropine (a parasympathetic test), and sweating (a sign of sympathetic cholinergic function) are intact. An upright posture and the administration of indirect-acting sympathetic drugs result in a doubling or tripling of plasma dopamine levels, and inhibiting dopamine synthesis raises the blood pressure. These data are consistent with the conclusion that sympathetic nerves release dopamine instead of norepinephrine in this disorder.

TABLE 3.—*Manifestations of Dopamine-β-Hydroxylase Deficiency ($n=6$)*

Symptom	*Frequency, %*
Severe orthostatic hypotension	100
Retrograde ejaculation	100
Ptosis	67
Complicated perinatal course	67
Nocturia	67
Hyperextensible joints	50
Nasal stuffiness	50

Evaluation of Orthostatic Hypotension

Patients with any form of orthostatic hypotension usually present with similar symptoms. On assuming an upright posture they may experience lightheadedness, dizziness, syncope, swaying, focal cerebral ischemia manifested by receptive or expressive aphasia or seizures (usually clonic jerks), angina pectoris, headache referred to the back of the head or neck, or tunnel vision. Symptoms and the likelihood of syncope are increased after meals, in hot environments such as after showers, and after consuming alcohol. With syncope, patients typically awaken almost immediately after assuming a horizontal position, without drowsiness or postictal confusion. Additional complaints may include a parkinsonian syndrome, diffuse neurologic defects, recurrent urinary tract infections, intolerance to antihypertensive agents, sleep apnea, and hoarseness.

Physicians must first consider nonautonomic causes and reverse correctable factors causing orthostasis. About 50% of our consultations for orthostatic hypotension involve drugs, with antihypertensive or diuretic agents, tricyclic antidepressants, vasodilators, alcohol, nitrates, narcotics, major and minor tranquilizers, marijuana, nasal sprays, and diet pills the most common offenders.[21] Severe volume depletion should be obvious from the clinical setting and history; subacute volume contraction from pheochromocytoma, renovascular hypertension, Addison's disease, and overenthusiastic dialysis or diuresis should be considered. Tachyarrhythmias, bradyarrhythmias, and heart block should be apparent from the circumstances surrounding the syncope, and flushing due to carcinoid, pheochromocytoma, and mastocytosis may be present. If the history clearly indicates that symptoms occur while the patient is supine, orthostatic hypotension may be excluded as a cause. The presence of mitral valve prolapse, pregnancy, large venous varicosities, fever, gastrectomy, sympathectomy, and prolonged recumbency or weightlessness may also be revealed by the history. In the absence of

these conditions, the patient will usually have a primary or secondary form of autonomic failure, and the physician should obtain a history, signs, and symptoms of peripheral neuropathy. The nonautonomic causes of orthostasis typically present abruptly, in less than a month, whereas orthostatic hypotension occurring as a result of autonomic failure usually has progressed over a period of two to five years.

The physical examination of a patient in autonomic failure will show a fall in blood pressure of at least 25 mm of mercury systolic and 10 mm of mercury diastolic within a minute of assuming an upright posture, with an increase in heart rate usually less than 5 bpm and always less than 10 bpm. This change in blood pressure is coincident with the onset of symptoms and is reproducible. Virtually all other causes of orthostatic hypotension will result in a moderate to pronounced rise in heart rate when blood pressure falls. More than 50% of patients with autonomic failure have supine hypertension. The eye examination may reveal unequal or irregular pupils that may be strikingly miotic and unable to dilate with pain. The skin is pale and dry with anhidrosis, and evidence of weight loss is often present. Sphincter tone is usually decreased. Tremor, dysdiadochokinesia, rigidity, and paucity of movement may be present, with or without focal neurologic signs.

Autonomic Function Testing

Many tests of autonomic function are available (Table 4). During the physical examination, the patient's supine, seated, and standing (30 to 60 seconds after assuming the upright position) blood pressures should be noted. The length of time the patient can stand without symptoms of cerebral hypoperfusion occurring has important diagnostic and prognostic implications. Standing times in excess of 10 minutes indicate insignificant orthostatic hypotension, whereas patients whose symptoms occur in less than 60 seconds can rarely live at home without assistance. Variations in heart rate can be estimated during the examination by observing a sinus arrhythmia during respirations, heart rate increases and decreases during and after the Valsalva maneuver, and heart rate slowing with carotid massage. Hyperventilation for more than 30 seconds will reduce systolic blood pressure in patients with autonomic failure by more than 20 mm of mercury, with a decrease of less than 10 mm of mercury being normal.[28] Repeated blood pressure measurements after a meal will often show the systolic pressure to be reduced by 20 to 60 mm of mercury in patients with autonomic failure.

Formal autonomic function testing may differentiate the various forms of autonomic dysfunction by indicating the presence or absence of appropriate blood pressure and heart rate changes with deep breathing and to the Valsalva maneuver, an increase in blood pressure during isometric exercise (handgrip test) and in response to pain (cold pressor test), the presence of sweating, increased blood pressure during arithmetic computations, and supersensitivity to α- and β-adrenergic agonists. Such testing may also assess the function of the baroreceptor reflex response to increases and decreases in blood pressure and detect the absence of a parasympathetic nervous system (if atropine fails to increase the heart rate), the absence of the sympathetic nervous system (if tyramine infusion fails to increase blood pressure or elevate plasma catecholamine levels), and the presence of baroreceptor dysfunction (if the blood pressure varies only with the heart rate). Syncope produced by a passive upright posture on a tilt table may occur in patients with increased sensitivity of cardiac mechanoreceptors, who otherwise may have normal autonomic function.

Laboratory evaluations in addition to standard admission tests should include obtaining specimens with the patient supine and standing to measure plasma concentrations of norepinephrine, epinephrine, and dopamine, 24-hour urine catecholamine and metabolite levels, a urine porphyrin screen, blood gas determinations, a Holter monitor, and, in the presence of neurologic deficits, a computed tomographic scan or magnetic resonance imaging scan of the head. If deficits in cardiovascular reflexes are present, many patients also have a neurogenic bladder, and a postvoiding residual evaluation and a cystometrogram are warranted. If a peripheral neuropathy is suspected, tests appropriate to the disorders listed in Table 2 should be done, with emphasis on obtaining a rectal or gingival biopsy for the diagnosis of amyloidosis.

TABLE 4.—*Tests of Autonomic Function*

Test	*Normal Response*
Standing time	> 10 min
Orthostatic blood pressure (BP)	Systolic BP falls < 10 mm of mercury, diastolic BP rises or remains steady
Sinus arrhythmia/respiratory variation	Longest to shortest RR interval > 1.2
Valsalva maneuver	Baseline to shortest RR > 1.4
Carotid massage	Heart rate (HR) slowing > 10 bpm
Hyperventilation	BP decrease < 10 mm of mercury
Handgrip test/isometric exercise	BP increase > 10 mm of mercury
Cold pressor test	BP increase > 10 mm of mercury
Mental arithmetic	BP increase > 5 mm of mercury
Postprandial BP monitoring	BP decrease < 10 mm of mercury
Sweat test	Diffuse sweating
Orthostatic catecholamine levels	≥ Twofold increase on standing
Drug responses	
Atropine	Increased HR > 25 bpm
Phenylephrine	BP_{25} = 200 μg, HR decrease
Isoproterenol	HR_{25}, BP_{-25} = 5 μg
Tyramine	BP_{25} = 2 mg, increased norepinephrine level
Epinephrine eye drops	No change in pupil size

BP_{25} = 25 mm of mercury BP increase, BP_{-25} = 25 mm of mercury BP fall, HR_{25} = 25 bpm HR increase

Management of Chronic Orthostatic Hypotension

The goals of managing chronic orthostatic hypotension are to obtain adequate cerebral perfusion with the patient in the upright position, to avoid situations that promote orthostasis, and to minimize symptoms and side effects of therapy. Achieving these goals will mobilize bedridden or housebound patients, maximize their functional capacity, and improve their quality of life.[22,29]

Physical Measures

Patients with autonomic failure have inadequate renal sympathetic function and renin-angiotensin-aldosterone activity to retain sodium and maintain an adequate blood volume. Increased salt intake, particularly early in the day, to more than 150 mEq per day is helpful in balancing the large volume losses that accompany patients' profound nocturia. The nocturia may be reduced substantially by elevating the head of the bed 15 to 20 cm (6 to 8 in) with shock blocks. This will reduce many patients' supine hypertension and thereby minimize the pressure natriuresis they experience. Even in patients without supine hypertension, elevating the head of the bed will promote fluid retention and lessen the orthostasis. Rest during the daytime should likewise be in the reverse Trendelenburg position in bed or in a reclining chair. Patients should be cautioned to rise from the lying position in stages, particularly in the morning. Supine hypertension may also be avoided by drinking alcohol or consuming a small meal at bedtime.

TABLE 5.—*Situations to Avoid in Chronic Orthostatic Hypotension*

Large meals	Coughing spells
Prolonged recumbency	Hot weather
Isometric exercise	Rapid ascent to high altitude
Standing motionless	Hot baths or showers
Alcohol	Fever
Working with arms above shoulder level	Hyperventilation
Straining at stool or with voiding	

The central blood volume may be increased by physical measures as well. Wearing heavy support stockings or pantyhose (Jobst), with or without an abdominal binder, while upright will reduce the 400- to 700-ml fall in central blood volume caused by standing. Pressure garments should be removed before reclining to avoid supine hypertension and diuresis. Antigravity or antishock suits have also been advocated, but their practical usefulness is limited. Presyncopal symptoms while standing should be treated promptly by having the patient squat, use a small portable stool, assume a stooped posture, tighten the leg muscles, or sit down with the feet elevated. Low levels of exercise may be tolerated well as long as the temperature is cool. The ideal form of exercise is swimming because hydrostatic forces perfectly oppose the reduction in central blood volume caused by gravity.

Patient education is a key ingredient of the successful management of orthostatic hypotension, both for situations to avoid and for the means of handling low blood pressure. Table 5 lists various situations that should be avoided or modified to prevent orthostasis or syncope. In addition, alcohol use and ingesting large meals may produce substantial falls in blood pressure, so avoiding ethanol consumption and taking several small meals during the day may alleviate recurrent episodes of orthostasis. A rapid ascent to high altitude may provoke hyperventilation and exacerbate orthostasis.

The enhanced sensitivity of these patients to sympathomimetic amines has resulted in malignant hypertension and strokes after the ingestion of normal doses of over-the-counter cold preparations. Likewise, diet pills, nasal sprays, and eye drops should be used with caution, if at all. Vasodilators, β-agonists, and diuretic drugs also should be avoided. These patients are also at higher risk of adverse reactions to anesthesia, for many reasons: Positive pressure respiration impairs the return of blood to the heart and lowers the blood pressure, many anesthetic agents produce vasodilation, the respiratory drive may be abnormal, supersensitivity to vasoconstrictor agents may result in anesthetic catastrophes, the absence of vagal tone may alter the response to atropine, abnormal sweating and pupillary responses may impair adequate monitoring, and the adrenal gland may not react appropriately to surgical stress. For these reasons, we recommend preanesthetic placement of a Swan-Ganz catheter for monitoring cardiac filling pressures and close intraoperative and postoperative management of the patient until full consciousness is regained.[30]

Drug Therapy

The goals of drug therapy are to increase the circulating blood volume and to support the patient through periods of the day or situations likely to produce orthostasis. Table 6 shows the agents used for these purposes.

Fludrocortisone may be used to increase the blood volume and enhance the pressor sensitivity to vasoconstrictor agents. Doses of 0.1 mg once or twice a day, slowly increased to a total of 1 mg per day, may be helpful, but pedal edema, hypokalemia, and supine hypertension may limit the dose of this agent, and some degree of tachyphylaxis will develop. Patients with autonomic dysfunction are supersensitive to α- and β-adrenergic agonists, and these agents must be used at low doses with careful monitoring of blood pressure.[23,24] Pressor agents such as phenylpropanolamine, phenylephrine, ephedrine, yohimbine hydrochloride, and ergotamine tartrate will raise blood pressure for one to four hours, and a properly instructed patient may use these during the day. We have observed a desensitization in response to the direct-acting sympathomimetics, which may be restored after a drug holiday of a week to ten days. Yohimbine is of value

TABLE 6.—*Drug Therapy in Chronic Orthostatic Hypotension*

Volume-increasing agents	Preventers of postprandial hypotension
Fludrocortisone acetate	Caffeine
Vasopressin	Indomethacin
Sympathomimetics	Somatostatin
Phenylpropanolamine	Dopamine receptor antagonists
Phenylephrine	Domperidone
Ephedrine hydrochloride	Metoclopramide hydrochloride
Midodrine	Miscellaneous drugs
Amphetamines	Nonselective β-blockers
Ergotamine tartrate	Nighttime vasodilators
Yohimbine hydrochloride	
Clonidine hydrochloride	
Dihydroxyphenylserine	

in patients with the Shy-Drager syndrome and in patients less severely affected by the Bradbury-Eggleston syndrome because the drug potentiates the release of catecholamines from sympathetic nerve terminals. It is also of particular value in diabetic autonomic neuropathy because of its blood pressure-raising actions and its potentiation of insulin release.

Both indomethacin and caffeine have mild blood pressure-raising effects and may reduce postprandial hypotension approximately 50% by limiting the increase in splanchnic blood flow after meals. We routinely advise our patients to drink the equivalent of two cups of caffeinated coffee when eating a large meal. Clonidine may also exert dramatic pressor responses in these patients because of its peripheral α_2-adrenergic agonist actions, but dry mouth and sedation have limited the number of patients who may be successfully managed with this agent.[31] Somatostatin and its analogues raise the blood pressure somewhat and antagonize postprandial hypotension but require intradermal injection.

Nasal insufflation of vasopressin has also been advocated both for its volume-retaining and its vasoconstrictor actions, but with prolonged use patients are prone to the development of electrolyte disorders. Nonselective β-blockers are often useful in milder cases because the β_2-antagonism prevents vasodilation in muscle vascular beds, thereby limiting the fall in blood pressure with an upright posture and exercise.

Nighttime supine hypertension can be reduced by a bedtime snack, a glass of wine, or short-acting vasodilators such as hydralazine hydrochloride or small doses of nifedipine. Vasodilators should be used with caution, however, because patients will usually continue to experience nocturia. Antihistamines have little effect on blood pressure in patients with autonomic failure but are the mainstay of therapy in patients with systemic mastocytosis. Levodopa often aggravates orthostasis in patients with parkinsonian symptoms, and occasionally the use of a combination of levodopa and carbidopa reduces the extent of drug-induced orthostasis. Investigational approaches to therapy in patients with autonomic failure have included posture-activated norepinephrine pumps and atrial tachypacing, but these appear to offer little practical benefit. Atrial tachypacing combined with β-blockade may alleviate much of the disability in patients with baroreceptor dysfunction.

A few patients with orthostatic hypotension have elevated plasma dopamine levels and may benefit from dopamine antagonists, such as metoclopramide hydrochloride or domperidone, or from the inhibition of dopamine synthesis by metyrosine.[1] The defect in norepinephrine synthesis present in patients with dopamine-β-hydroxylase deficiency may be circumvented by treatment with dihydroxyphenylserine, which is decarboxylated within sympathetic neurons directly to norepinephrine.[1]

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Eating Disorders
A Review and Update

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Anorexia nervosa and bulimia nervosa are prevalent illnesses affecting between 1% and 10% of adolescent and college age women. Developmental, family dynamic, and biologic factors are all important in the cause of this disorder. Anorexia nervosa is diagnosed when a person refuses to maintain his or her body weight over a minimal normal weight for age and height, such as 15% below that expected, has an intense fear of gaining weight, has a disturbed body image, and, in women, has primary or secondary amenorrhea. A diagnosis of bulimia nervosa is made when a person has recurrent episodes of binge eating, a feeling of lack of control over behavior during binges, regular use of self-induced vomiting, laxatives, diuretics, strict dieting, or vigorous exercise to prevent weight gain, a minimum of 2 binge episodes a week for at least 3 months, and persistent overconcern with body shape and weight. Patients with eating disorders are usually secretive and often come to the attention of physicians only at the insistence of others.

Practitioners also should be alert for medical complications including hypothermia, edema, hypotension, bradycardia, infertility, and osteoporosis in patients with anorexia nervosa and fluid or electrolyte imbalance, hyperamylasemia, gastritis, esophagitis, gastric dilation, edema, dental erosion, swollen parotid glands, and gingivitis in patients with bulimia nervosa.

Treatment involves combining individual, behavioral, group, and family therapy with, possibly, psychopharmaceuticals. Primary care professionals are frequently the first to evaluate these patients, and their encouragement and support may help patients accept treatment. The treatment proceeds most smoothly if the primary care physician and psychiatrist work collaboratively with clear and frequent communication.

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Anorexia nervosa and bulimia nervosa are illnesses with many causes involving developmental, family dynamic, and biologic factors. Their treatment requires an eclectic, individualized approach using a broad range of therapies. Primary care professionals are often involved in the initial evaluation and treatment of the symptoms and medical complications of these illnesses. In addition to recognizing the eating disorder syndrome and treating the medical sequelae, primary care practitioners have an important role in referring patients for psychiatric treatment and in encouraging them to accept such treatment.*

Diagnosis and Epidemiology

The criteria for diagnosing anorexia nervosa and bulimia nervosa are listed in Tables 1 and 2.[1] Over the course of their illness, patients may alternate between anorexia nervosa and bulimia nervosa. Of patients who meet diagnostic criteria for bulimia nervosa, estimates are that 30% to 80% have histories of anorexia nervosa.[2] The prevalence of anorexia nervosa is estimated to be 1% of young women with a bimodal pattern of onset; the peaks of onset occur at 13 to 14 and 17 to 18 years of age.[3] Bulimia nervosa is more common and affects between 4% and 10% of adolescent and college-age women.[4-7]

Many women who do not meet the strict diagnostic criteria nevertheless experience some symptoms of eating disorders such as preoccupations with food and weight.[4] Binge eating has been reported in 79% of female college undergraduates, and more than 50% of women in America report that they are dieting.[8]

Patients with eating disorders are often secretive about their eating behavior and come to the attention of primary care physicians only when others become concerned and insist on a medical evaluation. Anorexic patients often hide food, abuse laxatives, diuretics, or both, exercise excessively, and adamantly deny their symptoms or any need for treatment. Patients with bulimia nervosa are even harder to recognize; overt physical changes usually are absent, and patients often go to great lengths to conceal their behavior.

Although they are more common in women, both of these disorders also affect men. Approximately 5% to 10% of patients with anorexia nervosa are men, and the disorder may be more common in gay men.[9-11] The prevalence of bulimia nervosa is estimated to be 0.2% of adolescent and young men, and men represent 10% to 15% of all bulimic patients in community-based studies.[12]

Causes of Eating Disorders

Although many different theories for eating disorders have been proposed, none appear to be universally true.[4]

Development and Family Dynamics

As they grow up, anorexic patients often struggle for autonomy, identity, self-respect, and self-control.[4,13] An additional dynamic may be their fear or rejection of adulthood.[8]

*See also "Has Our 'Healthy' Life-style Generated Eating Disorders?" by Joel Yager, MD, on pages 679-680 of this issue.

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The families of anorexic patients may be enmeshed, overprotective, rigid, and poor at resolving conflicts.[8] In addition, the parents may have high expectations for their children to succeed and may place pressure on their children to meet these possibly unrealistic expectations.[14]

Bulimic behavior is posited by some authors to service unmet developmental needs. For example, Goodsitt proposed that the behavior reduces tension, helps regulate the self, and provides intense stimulation needed to dampen feelings of emptiness.[15] Personality traits of low self-esteem, self-regulatory difficulties, frustration intolerance, and an impaired ability to recognize and directly express feelings (anger in particular) have been described in patients with bulimia nervosa.[16] Varying degrees and forms of psychopathology have been described in the families of patients with bulimia nervosa, such as impaired cohesion, decreased structure, high levels of conflict, and overt negativity.[16]

TABLE 1.—*Diagnostic Criteria for Anorexia Nervosa**

- Refusal to maintain body weight over a minimal normal weight for age and height—for example, weight loss leading to maintenance of body weight 15% below that expected—or failure to make expected weight gain during period of growth, leading to body weight 15% below that expected
- Intense fear of gaining weight or becoming fat, even though underweight
- Disturbance in the way in which body weight, size, or shape is perceived—for example, the person claims to "feel fat" even when emaciated, believes that one area of the body is "too fat" even when obviously underweight
- In women, the absence of at least 3 consecutive menstrual cycles when otherwise expected to occur (primary or secondary amenorrhea) (A woman is considered to have amenorrhea if her periods occur only following hormone—estrogen—administration)

*From the American Psychiatric Association.[1]

Neurochemical Changes

Perturbations of the neurotransmitter and neuroendocrine systems are seen in persons with anorexia nervosa, although whether these neurochemical changes precede, accompany, or follow the behavioral changes is unclear.[17] The hypothalamic-pituitary-adrenal axis appears perturbed with findings of hypercortisolemia, nonsuppressive dexamethasone suppression tests, and increased cerebrospinal fluid (CSF) levels of corticotropin-releasing hormone.[18-20] Disruption of the neuroendocrine system is suggested by the finding that 30% to 50% of women with anorexia nervosa have amenorrhea before significant weight loss occurs.[21] The return of menses in these patients is often delayed until some time after weight is regained.[8]

A dysregulation of neuroendocrine and neurotransmitter systems may also play a role in bulimia nervosa. The brain monamine systems appear to be important modulators of appetite, mood, and neuroendocrine function, and researchers have found increased plasma concentration of β-endorphin, decreased plasma concentration of norepinephrine, and decreased CSF levels of the dopamine metabolite, homovanillic acid, in bulimic patients.[22,23] A particularly provocative finding pertains to alterations in cholecystokinin levels in patients with bulimia nervosa. In a study of bulimic patients, the cholecystokinin response to a meal and postprandial peak levels were found to be decreased when compared with controls, suggesting a potential dysregulation of the satiety mechanism.[24]

Morbidity and Mortality

Anorexia nervosa and bulimia nervosa can have substantial morbidity and mortality. Starvation itself disturbs sleep, impairs concentration, and causes indecisiveness, preoccupation with food, mood lability, irritability, anxiety, and depression.[25,26] Physical sequelae can include hypothermia, dependent edema, bradycardia, hypotension, and lanugo. Anorexia nervosa can also lead to infertility, osteoporosis, cardiac failure, and, ultimately, death.[19] Mortality has been estimated to be about 6% but was 20% in a cohort of patients observed for 20 years.[27,28]

For bulimia nervosa, potential medical complications include electrolyte and fluid imbalances, hyperamylasemia, hypomagnesemia, gastric and esophageal irritation and bleeding, gastric dilation, large bowel abnormalities (due to laxative abuse), edema, and fatigue.[29] Swelling of the parotid glands bilaterally, dental erosion, gingivitis, and knuckle calluses (from inducing vomiting using the fingers) are common physical signs of bulimic behavior.

Prognosis

The prognosis for persons with eating disorders is extremely variable. Some patients with anorexia may improve without treatment; for others, however, the course can be long and pernicious. After treatment, 50% of patients with anorexia nervosa may continue having persistent psychosocial impairment, and after achieving remission through successful inpatient treatment, about 50% may relapse within a year.[27,30] Authors have concluded that treatment does not clearly change the course of anorexia nervosa.[28,31]

Despite that bleak conclusion, clinicians can be guided by fairly well-defined good-versus-poor prognostic features. The prognosis for anorexia nervosa is more hopeful if the patient admits to feeling hungry, has positive self-esteem, is fairly mature developmentally, and has attained some autonomy.[28,32] Poor prognostic features include being ill with the disorder for more than six years, premorbid obesity, bulimic behavior, unstable personality, dysfunctional marriage, excessive somatic concerns, and lower minimum weight.[33]

TABLE 2.—*Diagnostic Criteria for Bulimia Nervosa**

- Recurrent episodes of binge eating—rapid consumption of a large amount of food in a discrete period of time
- A feeling of lack of control over eating behavior during the eating binges
- Regularly engages in either self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise to prevent weight gain
- A minimum average of 2 binge-eating episodes a week for at least 3 months
- Persistent overconcern with body shape and weight

*From the American Psychiatric Association.[1]

Prognostic features are less well defined for bulimia nervosa, but the long-term prognosis appears better than with anorexia nervosa. Most patients have an episodic course with an overall trend toward improvement.[28,34,35] A few patients with bulimia nervosa are resistant to treatment and have continuous, pernicious courses with extremely poor outcome.[28]

The prognosis is more hopeful if a patient is motivated for treatment, does not have concurrent disruptive psychopathology, and has good self-esteem.[4,36]

Eating Disorders and Mood Disorders

Controversy exists as to the relationship between eating and mood disorders. Estimates are that 40% to 80% of patients with eating disorders meet criteria for a lifelong history of depression.[8] Patients with eating disorders who have histories of depression tend to have families with histories of depression. Those without depressive histories themselves do not appear more likely than controls to have families with depression.[37] Understanding the nature of the relationship between mood and eating disorders is complicated by the potential for starvation itself to cause depression and by the potential for secondary depressions to be brought on by disruptive life events.[38]

Treating Eating Disorders

The treatment of eating disorders begins with the completion of a comprehensive, multidimensional evaluation.[4,39] Table 3 lists the areas that need to be addressed in this evaluation.[4] Obtaining as complete a history as possible is invaluable in planning treatment. In addition, various possible medical complications or concomitant psychiatric disorders must also be ruled out. The goals of treatment include medical stabilization, the control of abnormal eating behavior, an enhanced ability to identify and express emotions, and the prevention of relapse. Although this discussion focuses on the overall treatment as provided by psychiatrists and other ancillary specialists, primary care physicians need a basic knowledge of the treatment options available to make appropriate referrals once an eating disorder is diagnosed. Collaboration and close communication between the psychiatrist and the primary care physician are strongly recommended.

Anorexia Nervosa

Inpatient Psychiatric Treatment

Although many anorexic patients can be treated as outpatients, the following criteria have been defined to help clinicians decide whether inpatient psychiatric treatment is needed:

- Weight loss greater than 30% of ideal body weight;
- Persistent suicidal ideation;
- The need for withdrawal from laxatives, diet pills, or diuretics; and
- Lack of response to outpatient treatment.[39]

Before patients are discharged, they should show an improved ability to monitor diet and weight appropriately, manage a level of responsibility and activity similar to their home environment, and to achieve and maintain weight gain. Although in the past patients often required hospital stays of two to three months to accomplish these goals, the current economic climate of decreased coverage for psychiatric services has resulted in briefer stays. Therefore, once eating patterns are somewhat stable, patients are often discharged with subsequent close outpatient monitoring and treatment.

Correction of Starvation State

Primary care professionals can help psychiatrists to manage appropriately the refeeding of the anorexic patient in a starved state. Nutritional counseling and education of the patient are invaluable as this process is planned. Correcting the starvation state should be done gradually to prevent gastric dilation, pedal edema, and possible congestive heart failure.[28,40] Establishing an expected rate of weight gain—up to 1 kg (1 to 2 lb) per week—and a final goal weight is useful. Patients tend to do well initially with several small divided meals, with a gradual increase in the total amount of calories.[28] Tube feeding should be used only when absolutely necessary because of a life-threatening situation and is rarely required.[28]

Behavioral Treatment

One type of psychiatric treatment involves a behavioral approach that is efficacious, particularly early in treatment. With such an approach, patients participate in setting goals and defining positive reinforcers obtained on achieving these goals. Positive reinforcers may include, for example, increased autonomy, more privileges, and additional physical and social activities.[41,42] Overall, more lenient behavioral programs appear to be as effective as strict programs.[43] At Langley Porter Psychiatric Institute (San Francisco, California), patients and their primary nurse and therapist create and sign the written treatment plan that is then incorporated into the medical record. The plan is revised regularly as the treatment proceeds, with changes made based on a patient's progress.

TABLE 3.—*Assessing Eating Disorders*

Assessment	*Areas to Be Included*
History	
Eating disorder	Eating habits, rituals, behavior
	Body image
	Actual weight, desired weight, minimum and maximum weights
	Use of laxatives, diet pills, diuretics, emetics
	Presence of binge or purge behavior
	Menstrual history
	Use of exercise
Psychiatric	Include assessment for substance abuse, mood, anxiety, personality disorders, and suicidality
Past medical	
Family	Both medical and psychiatric
Examination	
Mental status	Suicidality and cognitive status
Physical	
Laboratory	Complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, phosphate, cholesterol, lipids, amylase, total protein, albumin, liver function tests, thyroid function tests, urinalysis, and electrocardiogram; consider tuberculin skin test, pituitary hormone levels, electroencephalogram, and chest x-ray film

Individual Psychotherapy

Individual psychotherapy is a critical adjunct to the behavioral focus, but such treatment is difficult until the starvation state is at least partially corrected. The technique of psychotherapy involves an empathic therapist who helps contain the patient's overwhelming fears of losing control and becoming fat.[28,31] Patients benefit most from a reassuring, supportive, and realistic therapist. In the course of the individual therapy, common themes uncovered include fears of failure and of independence, negative self-concepts, a dis-

torted body image, an inability or an impaired ability to identify and express emotion, and a denial of the illness.[39]

Family Treatment

Family therapy may also be recommended by the psychiatric treatment team. Families of patients with anorexia nervosa may show dysfunctional behavior and interactional styles such as overprotectiveness, enmeshment, rigidity, and poor conflict resolution.[44] An active, educational, and often directive therapeutic stance can identify and change the interactional structure of such families. Goals include providing mutual support, fostering healthy autonomy, restructuring positions within the family system, and decreasing guilty feelings.[28]

Group Therapy

An additional useful method for treating patients with anorexia is group therapy. Self-help groups with an educational focus can assist patients to gain an increased understanding of their illness and to confront their fears of losing control once they begin to gain weight. Psychotherapeutic group work can lead to a confrontation of intellectualization, an improved expression of feelings, and a gradual emergence of increased autonomy and competence.[45]

Medications

Various psychoactive medications have been used to treat patients with anorexia nervosa, but no single medication has proved to be dramatically effective.[28,46] The long-term effects of the various agents when used in this population are unknown, and they are best thought of as an adjunct to the therapies already discussed. No real basis exists for the use of antipsychotic agents unless the patient has concomitant psychotic symptoms.[28] Anxiolytics may be useful in reducing panic and anxiety associated with fears of losing control and gaining weight.[47] The mood stabilizer lithium carbonate has been reported to show efficacy.[48] Because of its potential to cause weight gain—which may adversely affect patient compliance—and its possible toxicity in patients who binge and purge, lithium should be used with caution in this population.

Antidepressants have not proved to be effective in treating anorexia nervosa,[28,46] but a trial should be considered if depressive symptoms persist despite weight gain or if the patient has concomitant severe depressive, panic, or obsessive symptoms.[39] If used, antidepressants need to be prescribed cautiously at low initial doses with a slow upward titration because these patients tend to be extremely sensitive to adverse effects. Vital signs should be closely observed, and, because toxic serum concentrations may develop at relatively low doses, levels should be periodically checked.[47]

Bulimia Nervosa

Inpatient Psychiatric Treatment

Most patients with bulimia nervosa can be treated as outpatients, but active suicidal ideation, severe depression, marked electrolyte or fluid imbalance, and the need to be withdrawn from laxatives, diuretics, emetics, or diet pills are all indications for considering inpatient psychiatric treatment.[28] In addition, resistance to outpatient treatment or the failure of such treatment also mandate evaluation for admission. Discharge criteria include increased control over the abnormal eating behavior, correction of any underlying metabolic derangements, and a resolution of acute suicidality.

Behavioral Treatment

The initial goal of treatment is to break or to decrease the binge-purge cycle. Self-monitoring and self-reporting are key components in establishing a treatment plan. Patients should participate in identifying specific behavioral goals and positive and negative reinforcers. The prescription of regular eating patterns and of preventing the purge response to eating, coupled with much support and education, are also important components of the treatment plan.[49]

Individual Psychotherapy

The initial treatment of bulimia nervosa focuses primarily on the behavioral and cognitive restructuring techniques necessary to combat a patient's abnormal eating patterns. Other useful techniques include relaxation training, nutritional counseling, assertiveness training, and supportive psychotherapy.[50] Common themes in the work include improving a patient's low self-esteem, self-consciousness, poor recognition and identification of feelings, low frustration tolerance, and poor impulse control.

Family Treatment

Dysfunctional interactional styles have been described in some families of patients with bulimia nervosa.[8,21] Family treatment may help to improve the cohesion and structure of the family and to decrease the level of conflict. Therapists often use an active, educational, and directive style to improve communication within the family.

Group Therapy

Group therapy is also useful. The self-help organization Overeaters Anonymous was founded in 1960 to help persons with compulsive overeating and now has specialty groups focused on issues unique to those with bulimia nervosa. Psychotherapy groups use an eclectic approach including cognitive-behavioral, psychoeducational, explorative, and supportive techniques. Some of the specific techniques suggested include keeping detailed food diaries, learning goal setting, educating patients about the psychology and biology of bulimia nervosa, and relaxation training.[4]

Medications

Unlike with the treatment of anorexia nervosa, medications can be useful in treating bulimia nervosa. In general, doses should be cautiously determined, the patient should be carefully assessed for suicidal ideation, the therapist should be cognizant of the potential for binge-purge behavior to exacerbate side effects, and blood levels when available should be monitored for the particular medication.

Antidepressants appear to decrease binge-purge behavior, improve attitudes about eating, and attenuate the patients' preoccupation with food and weight.[51] Several double-blind studies have shown notable improvement in patients treated with antidepressant drugs, but abnormal eating patterns may continue after treatment.[52] Antidepressant drugs studied have included amitriptyline hydrochloride, mianserin hydrochloride, imipramine hydrochloride, desipramine hydrochloride, and phenelzine sulfate.[53-58] A recent review of both open trials and controlled studies with fluoxetine reported notable improvement with this agent as well.[59]

Antidepressants appear to be effective in these patients regardless of a concomitant diagnosis of depression. In a follow-up study of 36 patients, Edelstein and colleagues reported that outcome after treatment with antidepressants was not related to Beck depression scale scores.[60] Similarly, patients treated with phenelzine were reported to improve substantially when compared with those who received placebo, and the presence or absence of depression had no bearing on the patients' improvement.[57]

Conclusion

Primary care physicians are often the first health care professionals patients with anorexia or bulimia see, and they must be aware of how patients with these disorders present. Primary care physicians also play a crucial role in making appropriate referrals and in encouraging their patients to accept psychiatric treatment. Although working with this population can be challenging, helping them to regain control over their pathologic eating behavior can be gratifying and rewarding.

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Epitomes

Important Advances in Clinical Medicine

Physical Medicine and Rehabilitation

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in physical medicine and rehabilitation that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Late Effects of Poliomyelitis—An Update on Fatigue and Weakness

MOST CLINICIANS KNOW by now that some polio survivors have troublesome new symptoms. Commonly described complaints include unaccustomed fatigue, worsening weakness in previously affected muscles, joint and muscle pain, cold intolerance, and worsening respiratory problems. Of the 711 polio survivors seen in one clinic in the past ten years, 562 (79%) had profound fatigue and 412 (56%) had new weakness.

Electrodiagnostic studies have shown that all polio survivors have chronic denervation and reinnervation with defective neuromuscular transmission, yet not all polio survivors have fatigue. Recent strength and endurance testing shows that symptomatic patients who have had polio have greater residual weakness, have reduced work capacity, and recover strength less readily after activity than asymptomatic ones. Furthermore, the clinical observation that polio survivors take three to four times longer to convalesce after an illness, operation, or trauma suggests that in some, deconditioning of old reinnervated motor units plays a role in the development of fatigue. Finally, worsening weakness and atrophy (postpolio muscular atrophy) may result from overwork, depending on the number of surviving motor units available to do a particular function and the intensity of the work.

A greater understanding of the pathophysiology of the neuromuscular deficits of polio survivors has resulted in a more sophisticated approach to the symptomatic management of fatigue and weakness in these patients. Studies have shown that symptomatic polio survivors can exercise without neuromuscular injury by interspersing periods of exercise with rest breaks (pacing). Patients are cautioned not to push themselves to the point of exhaustion and are instructed in pacing their day-to-day activities. Where indicated, energy conservation may be augmented with environmental modifications or the use of adaptive equipment. Polio survivors whose fatigue is compounded by deconditioning after an illness, operation, or trauma can safely improve their cardiorespiratory responses without injury to the motor unit with carefully paced and monitored aerobic exercise. Worsening weakness caused by overwork (postpolio muscular atrophy) is best treated by resting the overworked muscle group. A loss of strength and disuse atrophy after casting for a fracture can be successfully restored following the guidelines for nonfatiguing strengthening exercise for polio survivors.

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Prophylaxis and Treatment of Posttraumatic Epilepsy With Phenytoin

WITHIN FIVE YEARS of injury, posttraumatic epilepsy will develop in 2% to 12% of patients with moderate or severe traumatic brain injury. The incidence may be as high as 35% in those with severe injury who have an acute intracranial hematoma. Diagnostic tests, such as an electroencephalogram, do not predict the patients in whom epilepsy will develop. The lack of screening tests for high-risk patients has led physicians to use phenytoin to prevent epilepsy after brain trauma. Concern has since been raised about adverse cognitive effects of phenytoin therapy. Recent studies have failed to show the efficacy of anticonvulsant therapy for prophylaxis, however. They also have shed light on the choice of anticonvulsant for the treatment of epilepsy once it develops after brain injury.

Phenytoin prophylaxis was traditionally administered for a year after an injury, because half of those in whom posttraumatic epilepsy develops have their first seizure during that time. Prophylaxis has never been shown to protect against a later development after phenytoin therapy is discontinued. Over the past ten years, doubt has been raised about whether phenytoin prophylaxis is even effective at suppressing seizures during the treatment period. In a recent large, randomized, double-blind study of phenytoin prophylaxis after severe brain injury, no difference in the frequency of late seizures was found in the treated and untreated groups. Its use did suppress seizures occurring in the first week, however.

Serial examinations of these patients showed that phenytoin use had acute adverse effects on cognition in those with the most severe brain injuries. Despite these findings, there is no evidence that the adverse effects of phenytoin use exceed those of other anticonvulsants. In studies of patients with other forms of epilepsy, the cognitive effects of various anticonvulsants have been found to be subtle and overlapping. The greatest impairments are seen with timed tasks; these worsen with increasing serum drug levels, even within the therapeutic range. A comparative evaluation of anticonvulsants is needed because these patients differ from those with other forms of epilepsy who have more stable cognition.

The implications of these studies for clinical practice are as follows. Long-term phenytoin prophylaxis after traumatic brain injury is no longer warranted in the absence of a clinically definable seizure disorder. Prophylaxis during the first week after injury can suppress early seizures at a time when brain metabolism and blood flow may be compromised. After a week, phenytoin prophylaxis should be discontinued. If seizures do develop, many factors need to be considered, including ways to enhance compliance and to minimize cognitive side effects, especially during rapid phases of recovery. Regardless of which drug is chosen, the lowest dose necessary to control seizures should be used to minimize cognitive side effects.

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Neurobehavioral and Family Functioning Following Traumatic Brain Injury in Children

TRAUMATIC BRAIN INJURY is a major cause of morbidity in children and accounts for more than 100,000 admissions to hospital per year. Children who survive moderate and severe head trauma are at risk for immediate and lasting neurobehavioral sequelae that can interfere with their reintegration into school, affect peer relations, and cause family dysfunction. Recent studies have identified useful early predictors of outcome and have provided evidence that the magnitude of neuropsychological impairment is directly related to the severity of the brain injury.

The immediate consequences of traumatic brain injury depend on a number of factors, including the severity of the brain injury and the presence of extracranial injuries, particularly cardiac, chest wall, and intra-abdominal ones. The lower the initial Glasgow Coma Scale score and the longer the duration of coma, the greater the risk of permanent neurologic and cognitive impairment. Favorable prognostic indicators include the absence of early hypoxemia and a prolonged elevation of intracranial pressure, a Glasgow Motor Scale score of 4 to 6 at 72 hours, a coma of less than 24 hours, and posttraumatic amnesia of less than 2 weeks. Children with mild traumatic brain injury—initial Glasgow Coma Scale score of 13 to 15—account for more than 80% of all pediatric head injuries, but they generally have no serious compromise of educational function.

A recent investigation compared the early neuropsychological and academic outcome of a cohort of children with traumatic brain injury with that of controls individually matched on various premorbid characteristics. The assessments on these patients aged 6 to 15 years were undertaken three weeks after full orientation was achieved. The pattern of greater performance decline with increasing severity of brain injury was consistent for measures assessing intelligence, memory, speeded motor performance, adaptive problem solving, and academic performance. Moderately (Glasgow Coma Scale 9 through 12) and severely (Glasgow Coma Scale 3 through 8) injured patients performed at normal to low-normal levels in reference to standardized intellectual norms, but they showed substantial impairment when compared with their matched controls. Striking early deficits in the rate of information processing, speeded motor performance, and graphomotor dexterity have particular educational implications.

The same investigators examined the effects of injury severity on family functioning and determined preinjury factors that were most predictive of family outcome three months and one year following injury. Overall global family functioning was well maintained a year after injury in families of children with mild and moderate traumatic brain injuries. Families of children with severe traumatic brain injuries, however, showed substantially higher levels of stress and strained family relationships at follow-up. Functioning of the family before injury consistently emerged as the single most important predictor of family outcome.

These studies identify those children and families at greatest risk for sequelae after childhood traumatic brain injury. Families at risk for future problems can be identified at the time of injury and provided with ongoing support and referral services as early as possible. Targeting those children with moderate and severe traumatic brain injuries for early multidisciplinary rehabilitative support and careful follow-up of neuropsychological, psychosocial, and educational progress may minimize long-term morbidity.

Studies of the consequences of head injuries should be interpreted with caution if carefully and appropriately matched control groups are not included. Without the use of properly selected controls, it is difficult to distinguish between postinjury deficits caused by premorbid characteristics versus those caused by the brain injury per se. In addition, a child's actual deficits may be masked and valuable services withheld if postinjury performance is considered only in the context of population-based norms.

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Treatment of Postconcussion Syndrome

THERE CONTINUES TO BE much controversy regarding the cause and classification of the postconcussion syndrome. It has been thought of as a subset of the broader classification of mild head injury where initial Glasgow Coma Scale scores in such patients range between 13 and 15. It has been suggested that the postconcussion syndrome results from injuries in which a patient may have been initially "dazed" to having a brief coma. The syndrome typically consists of some combination of the following that persist after head trauma: headaches, fatigue, dizziness, blurred vision, difficulties in concentration, increased sensitivity to noise and light, irritability and emotional lability, recent memory difficulty, anxiety, and sleep disturbance. Many patients have persistent headaches, memory problems, and dizziness for a year after their injury. Persisting symptoms after a mild head trauma are frequently assumed to be a function of psychological overlay to the injury itself, pending litigation, or the presence of medically undetectable diffuse axonal injury. What makes diagnosis and subsequent rehabilitation difficult in many cases of postconcussion syndrome is the lack of evidence for craniocerebral injury by diagnostic imaging, neurophysiologic measurements, or neurologic examination.

Cases of the postconcussion syndrome bear a strong resemblance to those of chronic pain syndromes. In fact, the rates of chronic pain problems in this population are high. For example, chronic headaches occur in 89% and chronic upper extremity syndromes in 51% of those with postconcussion syndrome and are judged to be of a myofascial origin. Furthermore, many of the clinical features of the syndrome are similar to those of chronic pain and other chronic illnesses such as the irritable bowel syndrome and chronic fatigue syndrome. Common features that are shared among all of these syndromes are the frequent lack of diagnostic findings, a strong conviction of illness on the part of the patient, the existence of incentives for maintaining disability behaviors, the coexistence of depressive disorders, a social reinforcement of disability behaviors by significant others in the patient's home environment, and involvement by many health-care professionals. Given these sets of patient problems and behaviors, the treatment of patients with the postconcussion syndrome can be approached in a similar manner to those with chronic pain and chronic illness.

Centralizing treatment under one facility or primary care physician lessens the chance of care being fragmented. Early mobilization and physiotherapy for general aerobic conditioning and endurance are recommended. Trials of antidepressant medications combined with behavioral interventions that support physical reactivation, decrease illness behaviors, and lessen the effects of social reinforcement for illness can be useful with these patients. Consulting with a speech pathologist or neuropsychologist can be helpful with cognitive complaints. Finally, aggressive vocational rehabilitation efforts can be implemented early after the injury to reduce lost work productivity and to educate employers regarding the natural history of the syndrome.

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Family Support and Stroke Rehabilitation

THE DEVASTATING CONSEQUENCES of stroke affect the family as well as the patient. Relationships are disrupted, and family members take on roles unfamiliar to them. Questions about medical treatments, prognosis and the extent of recovery, financial management, and the new or heightened need for a care giver must all be urgently decided. Family involvement is becoming more important as more stroke patients are being cared for at home after discharge. The degree of a patient's recovery is directly related to the degree of psychological adjustment by care givers. This adjustment is determined more by a family's past ability to cope than by the severity of a patient's deficits at hospital discharge. A family's emotional distress may be expressed as increased hostility and criticism of the patient or with overinvolvement. The patient's adjustment to the disability is impaired as a result, and function deteriorates, compounding the likelihood of a poor recovery.

Depression frequently occurs in care givers. The incidence of depression in spouses of stroke patients is about 2½ to 3½ times greater than in controls. Factors leading to depression revolve around the stresses associated with new responsibilities that family member(s) must shoulder. The need for constant supervision and assistance, nursing care, and the assumption of full financial responsibilities for the family can be unmanageable without adequate preparation and support. These responsibilities lead to a constellation of decreased personal time, companionship, and social interactions outside the home. Marital discord and family conflicts grow. The patient's impaired judgment, safety, and insight complicate interactions with the care giver. Approaches to solving problems are often met with resistance and irrational demands by the patient, rather than the acceptance of compromises the family may offer.

The health professionals caring for a stroke patient can work together to address the concerns and needs of the family and to facilitate the transition home during this stressful time. Each member of the integrated team plays an essential role in educating the family. Families are most concerned with the neurologic and cognitive deficits present in their family member and the prognosis for future functioning or the extent of disability. These issues can be addressed by the physicians and nursing staff with careful explanations in lay terms of the various aspects surrounding the stroke.

Family counseling and education are essential. Individual sessions and family support groups can be led by licensed clinical social workers and neuropsychiatrists. This is an area requiring heightened attention in planning rehabilitation programs. The family also needs information from the case manager or social worker regarding the availability and means for getting financial, psychological, and physical (attendant) care assistance in the community. Referrals for outpatient programs such as adult day health care centers can be essential. These programs provide therapeutic activities, opportunities for social interaction and counseling for the patient, and respite for care givers after discharge.

All team members can provide a supportive and educational role. Defining the family's goals for the patient (and themselves) should be initiated early during the rehabilitation course, when the team's plans and goals for treatment are established. The therapists can instruct the family how to assist the patient in various activities of daily living, transfers, ambulation, and communication. Medication regimens, bowel and bladder management, and skin care can be taught by the nursing staff.

It is important for the rehabilitation team to incorporate the family into the care of the stroke patient and the careful planning for the return home for a smoother, less stressful transition and readjustment. The role of a comprehensive rehabilitation program becomes evident to this end. The better adjusted the family is to the consequences of the stroke, the better the physical and emotional recovery the patient will likely make and maintain after discharge.

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Focal Dystonia in Musicians

DYSTONIA IS A SPECIFIC type of involuntary movement characterized by sustained muscle contractions, often causing twisting and repetitive movements. Although dystonic movements can be seen secondarily in a number of conditions, including inherited disorders, Wilson's disease, drug and heavy metal toxicity, and stroke, adult-onset dystonia is usually idiopathic and often starts and remains localized to a circumscribed body part. Well-known examples of focal dystonia are writer's cramp and blepharospasm, but similar dysfunctions occur in musicians' hands and facial muscles. The incidence of writer's cramp has been estimated to be 3 per 1 million person-years. The incidence of focal dystonia in musicians is not known, but about 10% of musicians seen in arts medicine centers have motor control problems.

For the better part of this century, the dystonias were thought of as functional, psychiatric syndromes. This view no longer predominates because objective findings have been shown. Although the diagnosis remains one of exclusion, in musicians symptoms may include weakness, a loss of control, the drooping of fingers, involuntary flexing and extending, difficulty relaxing, difficulty moving fingers off keys, and difficulty with rapid alternating, ascending, or descending patterns. Facial involvement manifests as difficulty with embouchure. Pain is not common. The abnormal movement is usually task specific and requires examining the patients as they play their instruments. Men are affected by a ratio of 2 to 1. A family history of movement disorders such as essential tremor and Parkinson's disease may raise the index of suspicion. There does not appear to be an association between handedness or number of years playing. A history of some earlier injury to the affected area, such as transient overuse from excessive practicing, is common. The yield is low from workup for an underlying disease, but any suggestion of nerve entrapment should be fully evaluated electrodiagnostically because there have been occasional reports of dystonia resolving following a surgical release. In general, only 5% of cases of dystonia resolve spontaneously.

The basal ganglia are thought to be the site of the disorder, but no identifiable lesions have been shown on imaging studies—computed tomography, magnetic resonance imaging—in musicians. Recently abnormalities in the normal pattern of reciprocal inhibition between agonist and antagonist muscles have been observed electrophysiologically. Instead of the normal, smoothly coordinated pattern of antagonist relaxation with agonist contraction, a defect in presynaptic inhibition occurs at the spinal level (possibly due to a disruption of descending control from the subcortical areas), resulting in an abnormal cocontraction seen clinically as a cramp or involuntary movement. These findings are not unique to dystonia but do provide objective evidence of central, neurophysiologic disturbance.

No single treatment has been consistently successful. Electromyographic biofeedback, manipulative and movement therapies (such as the Alexander technique), stretching and strengthening exercises, relaxation techniques, and laborious retraining of musical technique have been of some benefit in a few cases. Anticholinergics (trihexyphenidyl hydrochloride) have been the most effective medications. Administering botulinum toxin to the abnormally contracting muscle has been effective in reducing the involuntary contraction in several types of dystonia, most notably blepharospasm, torticollis, and spasmodic dysphonia. Results in instrumental musicians have been mixed because of unavoidable weakness and the need for repeated administrations.

The success of treatment in musicians depends largely on the playing requirements of each person. A better result can be expected for a section player than a concert soloist. Unfortunately, substantial compromises often must be made in repertoire, tempo, and overall performing availability. Patients should be encouraged to consider other outlets such as teaching, conducting, and composing. The best approach at this time combines physical, pharmacologic, and pedagogic measures.

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Venous Thromboembolism in Stroke

THE INCIDENCE OF deep venous thrombosis is greatly increased in patients who have survived a stroke. Its risk is higher in patients with the most severe leg weakness, and, in patients at highest risk who do not receive thrombotic prophylaxis, the incidence may be as high as 75%. Although most thrombi have been detected within the first week following a stroke, the risk of deep venous thrombosis continues after the acute phase. Almost a third of patients admitted to a rehabilitation hospital after a recent stroke have deep venous thrombosis that can be detected by impedance plethysmography, despite being unsuspected clinically. Stud-

ies have also reported new venous thromboembolism occurring during the course of inpatient rehabilitation.

The clinical diagnosis is unreliable, and no therapeutic decisions can be made without laboratory confirmation. Although venography is the diagnostic gold standard, impedance plethysmography and duplex scanning are sufficiently sensitive and specific to allow confirmation or exclusion of deep venous thrombosis.

Early reports did not distinguish between venous thrombi confined to the calf and proximal vein involvement. About 20% of calf thrombi will progress and extend into the proximal veins. Half of these proximal thrombi will embolize. In about 20% of cases with clinical pulmonary embolism, the event is fatal. The risk of pulmonary embolism in stroke patients not receiving prophylaxis is 10% to 20%.

Based on the high incidence of deep venous thrombosis and pulmonary embolism in patients with stroke, prophylaxis of venous thromboembolism is recommended for all patients with stroke admitted to hospital with weakness. Randomized controlled trials have provided conclusive evidence indicating the efficacy of subcutaneous heparin in low doses two or three times a day. The risk of thrombosis is reduced to about 20%. In patients for whom heparin therapy is contraindicated—for example, those with hemorrhagic stroke—the use of an external pneumatic compression device is accepted as a reasonable alternative.

Because there is a residual risk of venous thrombi for patients on prophylactic therapy, some authorities recommend monitoring for new late-onset thrombi with impedance plethysmography (for example, weekly), especially in patients judged to be at higher risk because of severe paralysis.

There have been reports of new late-onset thromboembolic events occurring months after a stroke. There is no uniform agreement on the optimal duration of prophylaxis, and no fixed time is recommended. Prophylaxis should probably be continued during the postacute phase until the risk of thrombi is judged to be low. The best assessment of risk is made on clinical grounds, including consideration of the degree of persisting leg weakness and ambulatory status.

If deep venous thrombosis or pulmonary embolism develops during the rehabilitation phase of care, the patient must be treated with full-dose intravenous heparin and warfarin sodium. Recent reports indicate that both heparin and warfarin therapy may be started together and that the heparin regimen may be discontinued when the prothrombin time is in the therapeutic range, usually around day 5 or 6. Patients should be confined to bed as soon as the diagnosis is made to reduce the risk of embolism. Rehabilitation measures may be continued without interruption, except for mobility activities including walking. There is a difference of opinion regarding the desirable duration of bed confinement following a diagnosis of acute deep venous thrombosis. Some authors allow patients out of bed without restriction once the heparin dose is therapeutic, as early as the day after heparin therapy is started. Such a short interval minimizes the interruption in a patient's rehabilitation program. Warfarin therapy should be continued for at least three months to reduce the risk of a recurrence of the venous thrombosis.

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Alerts, Notices, and Case Reports

Pseudothrombocytopenia in a Child With the Acquired Immunodeficiency Syndrome

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THROMBOCYTOPENIA is a well-described finding in children with human immunodeficiency virus (HIV) infection.[1,2] Similarly, hematologic toxicity attributed to zidovudine therapy may include thrombocytopenia in addition to neutropenia and anemia.[3-5]

Herein we describe the case of an HIV-infected child (Centers for Disease Control classification P2) on zidovudine therapy with pseudothrombocytopenia due to ethylenediaminetetraacetate (EDTA)-induced chelation that was initially attributed to HIV infection, zidovudine toxicity, or both.

Report of a Case

The patient, a 6-year-old girl with neonatal transfusion-acquired HIV infection, was enrolled in the AIDS [acquired immunodeficiency syndrome] Clinical Trials Group Study No. 051 of the National Institute of Allergy and Infectious Diseases in September 1989. In the ten months preceding enrollment into the study, she had three documented episodes of thrombocytopenia (platelet counts ranging from 46 to 89×10^9 per liter [46,000 to 89,000 per μl]), two of which were associated with fever and an infectious process—pneumonia and *Streptococcus pneumoniae* bacteremia. Normal platelet counts were observed between these episodes, however. On the day a regimen of zidovudine, 180 mg per m^2 every six hours, and intravenous γ-globulin or albumin placebo (double-blind) was started, a peripheral blood smear revealed a platelet count of 59×10^9 per liter with evidence of platelet clumping on microscopic examination. Twelve days later, a platelet count of 296×10^9 per liter was recorded, and the low platelet count due to clumping was attributed to a suboptimal specimen collection. Over the next 12-month period, recurrent intermittent thrombocytopenia prompted a lowering of the zidovudine dosages, but the recurrent thrombocytopenia did not resolve. In addition, no clinical bleeding was ever noted in the patient. The possibility of pseudothrombocytopenia was considered when persistent platelet clumping became evident.

(Wong VK, Robertson R, Nagaoka G, Ong E, Petz L, Stiehm ER: Pseudothrombocytopenia in a child with the acquired immunodeficiency syndrome. West J Med 1992 Dec; 157:668-670)

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To pursue the cause of the platelet clumping, blood was collected through a central line in the patient and simultaneously placed in a standard 5-ml EDTA-containing tube (Becton-Dickinson, Rutherford, New Jersey) and a 3-ml tube containing 0.5 ml of acid citrate dextrose (ACD) after informed consent was obtained from the parent. Complete blood counts were serially determined using a Coulter Counter Plus Jr automated cell counter over a two-hour period. Concomitant leukocyte histograms and smears were generated. Serum immune complexes were assayed by using a commercially available enzyme immunoassay (Diamedix, Miami, Florida). Platelet-associated immunoglobulin (Ig) G and IgM levels were determined with fluorescein-labeled anti-IgG and IgM antibodies and flow cytometry (Specialty Laboratories, Santa Monica, California).

Table 1 depicts the result of serial determinations of peripheral leukocyte counts and platelet counts for the EDTA- and ACD-anticoagulated specimens. Platelet counts of 152 and 161×10^9 per liter were initially noted in the EDTA- and ACD-anticoagulated specimens, respectively. After 105 minutes a rapid decrease in platelet counts to 42×10^9 per liter was noted in the EDTA-anticoagulated specimen but not in the ACD-anticoagulated specimen.

TABLE 1.—*Leukocyte and Platelet Counts in Specimens Anticoagulated With Ethylenediaminetetraacetate (EDTA) and Acid Citrate Dextrose (ACD)*

	Leukocyte Count, cells × 10^9/liter		Platelet Count, × 10^9/liter	
Time, min	EDTA	ACD	EDTA	ACD
0	3.8	2.9	152	161
15	4.4	3.0	98	157
35	5.4	3.2	60	153
60	5.7	2.9	49	154
75	5.8	3.0	45	161
105	5.7	3.1	42	149

The leukocyte counts rose from 3.8 to 5.8 cells $\times 10^9$ per liter over the 105-minute testing period in the EDTA-anticoagulated specimen, but remained in the range of 2.9 to 3.2 cells $\times 10^9$ per liter in the parallel ACD-anticoagulated specimen. Microscopic examination of the EDTA-anticoagulated peripheral blood smears revealed evidence of platelet clumping in all but the initial smear.

The associated neutrophil histograms revealed an abnormal leukocyte "shoulder" that increased with time but was not present in the ACD-anticoagulated specimen (Figure 1).

Serum immune complexes were not detected, although platelet-associated IgG and IgM were identified.

Discussion

Thrombocytopenia in HIV-infected children may result from immune-related phenomena,[1] splenic sequestration,[6] or antiretroviral medication.[3-5] Various therapeutic measures have included surgical (splenectomy) as well as medical (γ-globulin, steroid, dapsone, and antiretroviral) therapies.[6-8] It is therefore important to establish the cause of the thrombocytopenia to guide appropriate management and to avoid diagnostic and therapeutic misadventures. Pseudothrombo-

ABBREVIATIONS USED IN TEXT

ACD = acid citrate dextrose
AIDS = acquired immunodeficiency syndrome
EDTA = ethylenediaminetetraacetate
HIV = human immunodeficiency virus
Ig = immunoglobulin

cytopenia related to EDTA-anticoagulated blood has not to our knowledge been previously described in HIV-infected children and in this case resulted in unnecessary zidovudine dosage adjustment. The apparent rapid and dramatic decrease in platelet numbers noted in the EDTA-anticoagulated specimen but not in the parallel ACD-anticoagulated specimen confirmed the suspicion that the thrombocytopenia noted in our patient was artifactual. Pseudothrombocytopenia may be defined as a low platelet count due to laboratory artifact and may result from platelet satellitism,[9] giant platelet syndrome,[10] vasopressin infusion,[11] or an improper blood drawing technique.

Pseudothrombocytopenia has also been noted in patients with type IIB von Willebrand's disease[12] and in the serum of patients with antiplatelet antibodies.[13] Antibody-related pseudothrombocytopenia may result from cold agglutinins[14] as well as EDTA-dependent IgA, IgM, or IgG antiplatelet antibodies.[13,15]

Initially described by Shreiner and Bell,[16] the incidence of EDTA-induced platelet clumping has ranged from 0.09% to 1.9%.[17] Pegels and colleagues have demonstrated in vitro EDTA-dependent platelet agglutination due to IgG, IgA, and IgM antibodies in addition to EDTA-independent "cold" antibodies.[13] The EDTA-dependent platelet clumping occurred with EDTA concentrations as low as 0.3 mmol per liter and would react to platelets from normal donors but not in platelets lacking glycoproteins IIb or IIIa (or both), as in patients with Glanzmann's disease.

Older automated cell-counting devices—Coulter Model S and S-Plus—were unable to detect platelet clumping, whereas the Coulter Counter Plus Jr used in our laboratory showed a "high takeoff" or "shoulder" from the ordinate in the EDTA-anticoagulated specimen (which was not present in the parallel ACD-anticoagulated specimen). Conversely, a "leukocyte shoulder" may be present in the absence of platelet clumping.[18]

The initial intermittent thrombocytopenia present in our patient was not recognized as caused by platelet clumping, as large platelet clumps may have falsely simulated neutrophils, thereby failing to show a "shoulder" on the histogram. This possibility is supported by the apparent reciprocal increase in leukocyte counts, as measured by the Coulter Counter Plus Jr, with decreasing platelet counts in the EDTA-anticoagulated specimen. Of interest, pseudoleukocytosis associated with pseudothrombocytopenia has been described by others.[18,19]

Because EDTA-dependent pseudothrombocytopenia appears to be time dependent, as shown in our patient and by others,[15,19] the intermittent thrombocytopenia seen earlier in our patient's course may have been detected only when processing of the specimen was delayed.

In summary, the appearance of thrombocytopenia in an HIV-infected child should be evaluated for possible pseudothrombocytopenia due to EDTA-induced chelation. If an automated cell counter device is used, the presence of an early "shoulder" would suggest the possibility of platelet clumping. It should be remembered, however, that the leukocyte histogram "shoulder" may be absent despite platelet clumping. Consequently, microscopic examination of a peripheral blood smear from an ACD-anticoagulated specimen or from a finger-stick blood specimen would elucidate the presence or absence of platelet clumping and thereby avoid unnecessary medical and diagnostic misadventures.

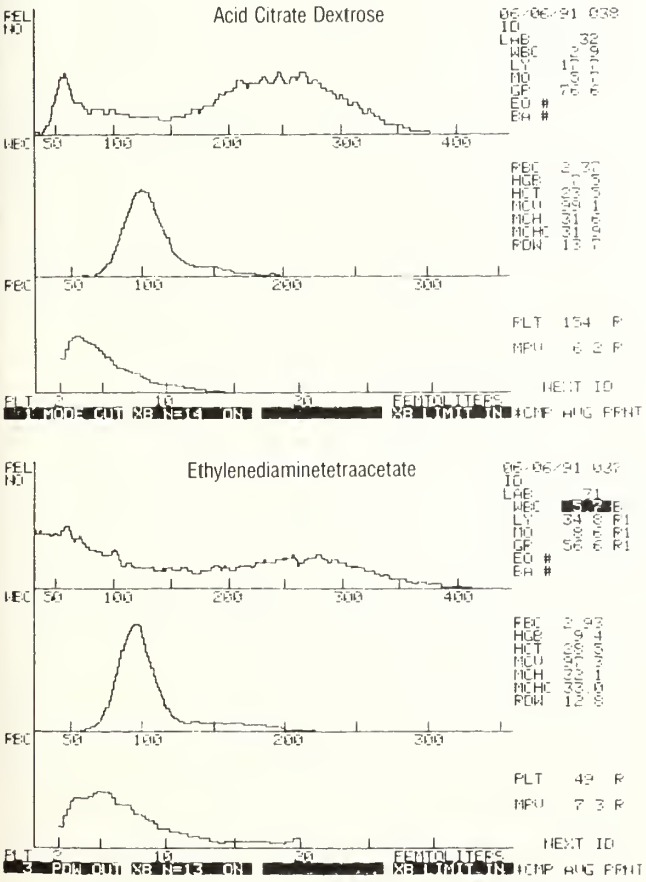

Figure 1.—Histograms (leukocyte [WBC], erythrocyte [RBC], and platelet [PLT] counts) are shown for blood specimens anticoagulated with acid citrate dextrose and ethylenediaminetetraacetate.

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Reflections on the Anion Gap in Hyperglycemia

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THE ANION GAP is the difference between measured anions and measured cations; it reflects primarily the unmeasured anions, those not identified by the usual electrolyte determination.[1,2] An increased anion gap generally indicates the accumulation of organic anions. To calculate the gap, the following formula is often used:

$$\text{Anion gap} = [Na^+] - ([HCO_3^-] + [Cl^-]) = 8 \text{ to } 16 \text{ mEq/liter}$$

Electrolyte determination using some of the new ion-specific electrode methods may yield a slightly lower range for the anion gap but does not alter the principle.[3]

A case of a patient with hyperosmolar coma and associated electrolyte abnormalities prompted us to question how the anion gap should be calculated in such situations. Specifically, should its calculation be modified in any way to account for the dilutional effect of severe hyperglycemia on serum electrolyte levels? To our knowledge this issue has not been addressed previously in the medical literature.

To answer this question we reviewed the primary literature on the anion gap, the acid-base status in hyperglycemic coma, and the physiologic principles underlying the dilutional hyponatremia seen in severe hyperglycemia. In addition, we conducted an informal survey to determine how other house staff and faculty at our institution (Stanford [California] University Medical Center) approached this problem.

(Varon J, Jacobs MB, Mahoney CA: Reflections on the anion gap in hyperglycemia. West J Med 1992 Dec; 157:670-672)

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Report of a Case

The patient, a 56-year-old woman with a history of non–insulin-dependent diabetes mellitus, presented to the hospital after being found incoherent by a relative. On arrival at the emergency department, the patient was lethargic but responsive to painful stimuli. Her blood pressure was 140/86 mm of mercury, heart rate 110 beats per minute, and respirations 24 per minute. There were blood pressure and pulse orthostatic changes. Physical examination findings were unremarkable except for a depressed mental state. Admission laboratory studies revealed the following values: serum glucose 87.4 mmol per liter (1,574 mg per dl), sodium 111 mmol per liter (mEq per liter), potassium 5.7 mmol per liter, chloride 76 mmol per liter, bicarbonate 17 mmol per liter, blood urea nitrogen 26.7 mmol per liter (74.7 mg per dl), and creatinine 177 μmol per liter (2 mg per dl). An arterial blood gas determination with the patient breathing room air showed a pH of 7.35, a Pa_{CO_2} of 36 torr, and a Pa_{O_2} of 82 torr.

Before the blood gas results were received, an attempt was made to analyze her acid-base status by calculating the anion gap. The admitting house staff was unsure as to whether and how this calculation should be done given the dilutional effect of profound hyperglycemia on the serum electrolytes.

Subsequently this case was presented to 33 house officers (internal medicine residents in postgraduate years 1 to 3) and 18 general internal medicine faculty. The written report was given, and they were asked to calculate the anion gap, to give the method for their calculations, and to analyze the acid-base status.

Results

Nearly a third of the faculty (5 [28%]) and a third of the house staff (11 [33%]) significantly exaggerated the magnitude of the anion gap by correcting the sodium concentration for the degree of hyperglycemia but neglecting to correct the other electrolytes. None of the house staff and only one faculty member corrected the anion gap for the dilution of all the electrolytes. Moreover, respondents uniformly misinterpreted an increased gap as synonymous with acidosis. Only 18 house staff (54%) and 6 faculty (33%) requested a blood gas analysis to confirm this impression.

Discussion

The central issue raised by this case is whether the calculation of the anion gap should be modified to correct for the dilutional effect of severe hyperglycemia on all the serum electrolytes, as is commonly done for the serum sodium level. To our surprise, we found that medicine house staff and faculty internists at our institution frequently exaggerate the anion gap in hyperglycemia by using a "corrected" value for the serum sodium but not for other electrolytes. Using two distinct lines of reasoning, we concluded that the anion gap should be calculated from the electrolytes as measured. The basis for this conclusion will be discussed further. In addition, we detected a common misconception that an increased anion gap is indicative of acidosis. The limitations of the anion gap in leading to this conclusion warrant review.

It is commonly understood that severe hyperglycemia is associated with a dilution of the serum sodium, which resolves as the glucose level is lowered. This phenomenon was first described by Seldin and Tarail in 1949.[4] Serum electrolyte levels are diluted by the movement of water out of cells

A $AG = [Na^+] - ([Cl^-] + [HCO_3^-]) = 111$ mEq/liter $- (76$ mEq/liter $+ 17$ mEq/liter$) = 18$ mEq/liter

B $Na_c = [1.6\ (Glucose - 5.5\ mEq/liter)] + [Na^+] = 135$ mEq/liter

C $AG_c = (Na_c/[Na^+]) \cdot AG = (135\ mEq/liter/111\ mEq/liter) \cdot 18 = 22$ mEq/liter

D $AG_{Nac} = Na_c^+ - ([Cl^-] + [HCO_3^-]) = 135$ mEq/liter $- 93$ mEq/liter $= 42$ mEq/liter

Figure 1.—The formulas and data used in the calculation of the anion gap (AG) in our patient are shown. Subscript "c" indicates correction for dilution by water shifting out of cells during hyperglycemia. $[Cl^-]$ = serum chloride concentration, $[HCO_3^-]$ = serum bicarbonate concentration, $[Na^+]$ = serum sodium concentration

along an osmotic gradient created by the addition of an impermeant solute such as glucose or mannitol.[5] To aid physicians in determining the degree of dehydration in severely hyperglycemic patients, it is helpful to transform or "correct" the measured serum sodium value to that which would be present after the resolution of the hyperglycemia. A commonly used correction is that for every 5.5 mmol (mEq) per liter of serum glucose greater than 5.5 mmol per liter, 1.6 mmol per liter should be added to the measured value of sodium to obtain the sodium concentration that would exist in the absence of hyperglycemia.[6] This correction factor was derived by calculating the serum glucose and sodium that would result after the addition of glucose to a hypothetical insulinopenic person. No calculations were made for other electrolytes.

Only the sodium value is typically corrected, as it is representative of the total body osmolarity and water balance. It is possible, however, that all the serum constituents are initially subject to the same dilution as the sodium.[7(p1341)]

In extremely hyperosmolal states, if the serum sodium correction alone is applied to the formula to determine the anion gap, patients will have a falsely and strikingly elevated gap (Figure 1-D). Thus, calculating the anion gap by correcting only the serum sodium value is clearly wrong.

Should the anion gap be calculated after correcting for the degree of dilution of all the electrolytes?

This question can be addressed on both practical and theoretical grounds. If it is assumed that all serum electrolyte levels are initially diluted in parallel with the sodium, the following formula derives to correct the serum chloride level, the serum bicarbonate value, and thus the anion gap (AG)[7]:

$$([Na^+]\ \text{corrected})/([Na^+]\ \text{measured}) \times (Cl^-,\ HCO_3^-,\ \text{or AG}) = (Cl^-,\ HCO_3^-,\ \text{or AG})\ \text{corrected}$$

This formula yields the maximal change in the anion gap that could be expected to occur before cells undergo adaptive volume-regulating increases.

With hyperglycemia (glucose levels in the range of 50 to 100 mmol per liter [900 to 1,800 mg per dl]), the corrected anion gap is increased by only 5% to 20%. Thus, in our patient, the anion gap of 18 mEq per liter would be increased to 22 mEq per liter (Figure 1-C). This small increase is unlikely to be clinically relevant. In fact, when we calculated the corrected anion gap in the only series where both the pH and the anion gap were provided, no improved discrimination of the severity of acidosis was obtained.[8] Thus, on practical grounds we would argue that this type of correction is unnecessary.

Theoretic considerations also argue against correcting the anion gap. The anion gap is not made up of a single element like sodium primarily limited to the extracellular compartment. Rather, it comprises several different ions, some of which are not limited to the extracellular compartment and whose behavior as water shifts in and out of cells is not predictable.

The exact nature of the increased anion gap in severe hyperglycemia has not been elucidated. Lactate levels are slightly elevated, but these account for only a small fraction of the gap.[8] Other contributing factors may include the hemoconcentration of albumin, renal insufficiency, mild ketosis, hyperphosphatemia, and the release of intracellular organic acids.[8,9]

As hyperglycemia resolves and water moves back into cells, some of these ions—such as phosphate and organic anions—are likely to shift back into cells and thus may not increase their extracellular concentration as does sodium. Adding to this complex situation is the fact that hypertonicity itself may alter the usual distribution and transport of ions across cell membranes. A clinical example of this is the acute hyperkalemia associated with severe hypertonicity.[10] Alterations of ion transport and the accumulation of intracellular organic ions, so-called osmolytes, allow certain cells to restore cell volume towards normal.[11-13] The net effect of these adaptive changes on serum electrolytes in human hyperosmolar coma is unknown. We do know, however, that in chronic hypotonic hyponatremic states, the sodium and chloride levels fall proportionately, whereas potassium and bicarbonate levels are maintained in the normal range.[13] Thus, at least in some chronic conditions, dilution of the sodium and chloride is not accompanied by a parallel dilution of bicarbonate. Given these considerations, we would argue on both practical and theoretic grounds that the simplest and most physiologic practice is to use the anion gap calculated from the electrolytes measured, with no correction for hyperglycemia.

Once the anion gap has been appropriately calculated, how should it be interpreted? First, it is important to emphasize that an increased anion gap is not synonymous with acidosis.[1,2,14] A study done to ascertain the diagnostic usefulness of an elevated anion gap found that only when it exceeded 30 mEq per liter was organic acidosis always identified.[14] It is not adequately appreciated that metabolic alkalosis itself is often associated with an increase in the anion gap, largely due to an increased lactate production and to increases in the concentration and negative charge on albumin.[2,8,9,15] An increased gap should simply be used to alert physicians to a possible acid-base problem and must be accompanied by measurement of the pH for proper interpretation.

The actual acid-base status of patients with hyperosmolar coma is variable. Although mild acidemia (mean pH of 7.30) is most frequently reported,[9,16] the pH was 7.35 or above in fully half the 20 patients reported by Arieff and Carroll and actually exceeded 7.42 in 5 of those.[8] The reported anion gap is also variable but tends to be elevated regardless of the pH. The mean anion gap was 34 mEq per liter in Arieff and Carroll's series and 23 mEq per liter in the patients reported by Gerich and co-workers.[8,17] Massive elevation of the anion gap, however (≥ 40 mEq per liter), was seen exclusively in patients with acidemia (pH ≤ 7.35). Conversely, acidemia

was rarely associated with a gap of 25 mEq per liter or less.

In our particular case, the calculation of the anion gap using a corrected serum sodium value but with no correction in the serum chloride or bicarbonate levels led many house officers and faculty members to think that the patient had a massively elevated anion gap and thus severe acidosis (Figure 1). In fact, the gap of 18 mEq per liter put her in the group of patients with hyperosmolar coma who are unlikely to have clinically important acidosis.

Conclusion

The anion gap should be calculated from the serum electrolytes as measured. Correction for the dilutional effect of hyperglycemia is unnecessary on practical grounds and probably unsound on physiologic grounds. Especially to be avoided is correction of the serum sodium value alone, as this will falsely exaggerate the gap.

Although hyperglycemic coma may be associated with a high anion gap, we must emphasize that an increased gap is not synonymous with acidosis. An increased anion gap is a clinical clue that requires a pH determination (together with clinical judgment) for an accurate interpretation of a patient's acid-base status. Venous blood gas determinations may be used for this purpose.[18]

It is hoped that a clear understanding of these concepts will diminish the likelihood of a misinterpreted acid-base status with the potential for incorrect therapeutic decisions.

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Carcinocythemia

A Terminal Manifestation of Metastatic Breast Cancer

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THE SPREAD OF solid tumor cells through the circulatory system, with the documentation of such spread on a routine Wright-Giemsa stain of peripheral blood smears, is an infrequent phenomenon.[1,2(p418)] In 1960 Finkel and Tishkoff noted blast cells in the peripheral smear of a 44-year-old woman with oat cell cancer of the lung.[3] Carey and co-workers were the first to use the term "carcinocythemia" to describe this phenomenon.[4] They noted a unique population of cells on a Wright's-stained blood smear of a patient with metastatic breast cancer. Histochemical stains were used to contrast these cells from those of a second patient with breast cancer in whom acute myelocytic leukemia developed as a late complication of chemotherapy and radiation therapy that she received for her cancer. I report a rare case of a patient with advanced breast cancer in whom carcinocythemia developed in the terminal phase of her illness.

Report of a Case

The patient, a 62-year-old woman, was admitted to Virginia Mason Medical Center (Seattle, Washington) in February 1991 because she had progressive shortness of breath and lethargy. Ten years earlier she underwent a right modified radical mastectomy for infiltrating ductal carcinoma. She received adjuvant chemotherapy consisting of cyclophosphamide, methotrexate, and fluorouracil. Three years later carcinoma in situ of the left breast developed, and she underwent a left modified radical mastectomy. A year later she had a left chest wall recurrence and was treated with doxorubicin-based chemotherapy followed by radiotherapy and tamoxifen therapy. In 1988 a biopsy again showed left-sided chest wall recurrence. Despite chest wall reconstruction, photon and electron radiation therapy, and subsequent chemotherapy—fluorouracil with leucovorin calcium modulation, mitoxantrone hydrochloride, cisplatin, and vinblastine sulfate—her tumor enlarged. In June 1990, she was placed on a regimen of aminoglutethimide, but six months later left chest skin biopsies confirmed the presence of progressive adenocarcinoma. The following week, she complained of shortness of breath and difficulty concentrating.

On admission the patient was confused, but the findings of a neurologic examination were nonfocal. Left supraclavicular adenopathy and subcutaneous left chest wall nodules were noted. Her hemoglobin level was 161 grams per liter, platelet count 100×10^9 per liter (100,000 per μl), and leukocyte count 13.9×10^9 per liter (13,900 per μl). The differential leukocyte count disclosed 0.42 lymphocytes, 0.09 bands, 0.33 segmented neutrophils, 0.11 monocytes, and 0.05 metamyelocytes. A blood gas determination with the patient

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breathing room air revealed an increased arteriolar-alveolar gradient with 85% hemoglobin saturation. A computed tomographic scan of the head was unremarkable, but a liver ultrasonogram showed multiple hypoechoic lesions consistent with metastatic disease. A serum ammonia level was modestly elevated, and lactulose therapy was begun, but the patient remained confused. Four days later the patient's breathing became acutely labored. A peripheral blood smear showed a leukocyte count of 23.9×10^9 per liter with 0.35 bands, 0.16 neutrophils, 0.23 lymphocytes, 0.08 monocytes, and 0.13 blast cells. The leukemialike cells possessed an increased nuclear-to-cytoplasmic ratio with hyperchromatic nuclei and measured between 18 and 22 microns in diameter (Figure 1). The large mononuclear cells in buffy-coat smears stained positive for carcinoembryonic antigen (Accurate Chemical and Scientific Corporation, Westbury, New York), epithelial membrane antigen (Accurate), and cytokeratin (Dakocytokeratin, Dako Corporation, Carpenteria, California; Figure 2) and negative for leukocyte antigens (Becton-Dickinson, Mountain View, California).[5-8] Despite a regimen of supplemental oxygen, fluids, and intravenous antibiotics, her condition rapidly deteriorated. She lapsed into coma and died the following morning. An autopsy was not done.

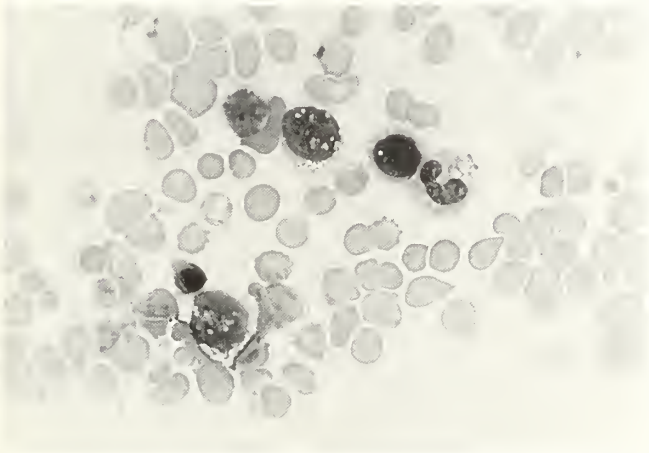

Figure 1.—Tumor cells in peripheral blood show increased nuclear-cytoplasmic ratio, the presence of nucleoli, and hyperchromatic nuclei (Wright-Giemsa stain, original magnification × 200).

Discussion

The presence of metastatic cancer cells in peripheral blood has been described for several decades.[1,3,9] The finding of a leukemialike picture with circulating nonhematopoietic malignant cells in the peripheral blood is, nonetheless, extremely rare. In a 1984 review of the English-language literature, Gallivan and Lokich found only ten reports of carcinocythemia or cancer-cell leukemia among patients with advanced carcinoma.[10] Four had oat cell carcinoma of the lung, two had carcinoma of the breast, and one each had adenocarcinoma of the ileum, rhabdomyosarcoma, carcinoma of the uteropelvic junction, and melanoma. The time of the onset of carcinocythemia to death varied from days to several weeks.

More recent reports have focused on distinguishing carcinocythemia from acute leukemia (de novo or secondary). Yam and Janckila used cytochemical, immunochemical, and concentration techniques to show that blast cells noted on the peripheral smear of a patient with disseminated breast cancer were epithelial and not hematopoietic cells.[11] Lugassy and associates described the cases of two patients in whom carcinocythemia developed as a late complication of breast cancer.[12] Cytologic examination of peripheral blood smears in both cases showed the presence of numerous large abnormal cells; in one case the cells simulated those of a Burkitt's lymphoma. Cytochemical or immunologic marker studies (or both) ruled out a hematopoietic origin of the malignant cells. In both cases, the patients died shortly after carcinocythemia was noted.

The mechanism invoked to explain the development of carcinocythemia remains unclear. In several cases where autopsies were done, the spleens were noted to be atrophic, heavily infiltrated with tumor, or absent, leading some to conclude that damage to the reticuloendothelial system impairs the removal of circulating tumor cells.[4,13,14] In at least two cases of carcinocythemia, however, autopsy studies failed to demonstrate overt splenic disease.[8,15]

The documentation of circulating cancer cells on a routinely prepared peripheral blood smear provides an unusual example of the hematogenous spread of solid tumors. The presence of circulating cells with increased size, high nuclear-to-cytoplasmic ratio, and an increased number of nucleoli in a patient with metastatic cancer suggests the development of carcinocythemia. It should be noted, however, that patients with malignant neoplasms treated with irradiation and chemotherapy are at increased risk for treatment-related myeloid leukemias to develop.[16,17] The tumor cells typically appear singly and in clumps, making a distinction from acute leukemia possible. Confusion may arise in small-cell carcinoma of the lung where tumor cells possess scant cytoplasm, circulate singly in the peripheral blood, and vary in size.[13] Additional confusion may be encountered when the marrow shows diffuse infiltration by tumor. Cytochemical and immunochemical studies such as those used in this case may further aid in characterizing these abnormal cells. Normal cells that only rarely are noted on a peripheral blood smear and may be confused with carcinocythemia include osteoclasts, megakaryocytes, and endothelial cells.[10]

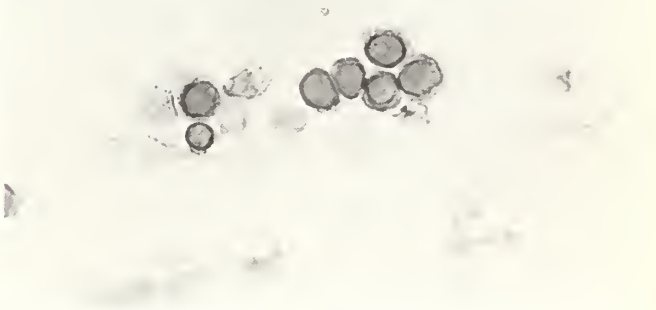

Figure 2.—A peripheral blood smear (buffy coat) shows a cluster of strongly reactive carcinoma cells with monoclonal antibodies to cytokeratin (immunoalkaline phosphatase method, original magnification × 200).

In reports that have mentioned the time from the onset of carcinocythemia to death, times have ranged from three days to eight months with a mean survival of less than four weeks

for patients with metastatic cancer. The rapidly fatal outcome observed in this patient serves to emphasize that carcinocythemia is a terminal manifestation of carcinomatosis.

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Radiologic Case

Thin-walled Lung Cavities and Cysts Due to AIDS-Related Pulmonary Infection

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 38-year-old man, a former intravenous drug injector, was admitted to hospital with a four-week history of fever, productive cough, bilateral pleuritic chest pain, exertional dyspnea, and a weight loss of 12 kg.

His leukocyte count was normal, but his CD4 count was only 22 cells per mm^3. His blood lactate dehydrogenase level was elevated. Sputum examination revealed no organisms on smear or culture. Multiple blood cultures showed no growth. An x-ray film done two years earlier was normal. A chest x-ray film (Figure 1) was done.

Figure 1.—The chest x-ray film shows patchy infiltrates over the apex, midzone, and base of the left lung. Bilateral multiple small thin-walled cavities are seen, especially over the periphery of the right lung (**arrows**). Several larger thin-walled cysts are present over the left midzone.

What are the findings?

What is the likely diagnosis?

How can the diagnosis be established?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

(Padmanabhan K, Vora S: Thin-walled lung cavities and cysts due to AIDS-related pulmonary infection. West J Med 1992 Dec; 157:675-676)

From the Pulmonary Disease Department, Coney Island Hospital (Drs Padmanabhan and Vora), Brooklyn, New York, and the State University of New York Health Science Center at Brooklyn (Dr Padmanabhan).

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ANSWER: Pneumocystis carinii *pneumonia*

PNEUMOCYSTIS CARINII PNEUMONIA is the most frequent pulmonary infection in persons with the acquired immunodeficiency syndrome (AIDS), occurring in 50% to 85% of patients. The most common radiographic findings are diffuse bilateral interstitial or alveolar infiltrates, seen in 48% to 86% of patients. Atypical radiologic features include localized infiltrate or consolidation, upper lobe predominance, nodular patterns, cavities, cavitating nodules, thin-walled cysts, pneumothorax, hilar adenopathy, and small pleural effusions. The occurrence of thin-walled cavities and cysts is being recognized with increasing frequency and has been described by chest radiographic film in 7% of patients and by chest computed tomographic scan in up to 40%. During the course of the same episode of pneumocystis lung infection, a variety of cysts can be seen radiologically and histologically. Small intraparenchymal thin-walled cavitary necrotic lesions can be seen interspersed with larger, less inflamed subpleural cysts. Mechanisms proposed for their development include direct tissue toxicity by the organism, alveolar distension from narrowed inflamed bronchioles, and local destruction due to prolonged elaboration of proteolytic enzymes such as elastase from persistently activated macrophages. The increased incidence of pneumothorax (9%) in patients with AIDS and *P carinii* pneumonia is probably related to the formation of such cysts, blebs, or pneumatoceles in a subpleural location.

Other forms of AIDS-related lung infection where similar radiographic features may be seen include septic emboli with right-sided endocarditis, nocardiosis, coccidioidomycosis, histoplasmosis, and tuberculosis. Though generally characteristic of mycobacterial lung disease, cavity formation is a rare finding in AIDS-related pulmonary tuberculosis.

Fluid obtained by bronchoalveolar lavage is an excellent specimen for staining and culture purposes to diagnose bacterial, fungal, parasitic, and viral infections in patients with AIDS and lung infection. Its sensitivity in detecting *P carinii* pneumonia is 79% to 98%. Sensitivity of induced sputum to identify the organism ranges from 55% to 79%. The diagnosis was established in our patient by the presence of numerous cysts of *P carinii* in methenamine silver staining of alveolar lavage fluid obtained by bronchoscopy. The elevated lactate dehydrogenase level and low CD4 blood counts are clues to the diagnosis.

In patients with lung infection and AIDS, or at risk for AIDS, the presence of new cavities or cysts on the chest film should strongly suggest a diagnosis of *P carinii* pneumonia. In seriously ill patients, empiric therapy for *P carinii* pneumonia is warranted until the infecting organism is identified.

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Commentary

Clinical Studies With Make-believe Drugs

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In late 1990, the Office of Technology Assessment (OTA) published a review of the most commonly used unconventional cancer treatments in the United States.[1] The report discussed the treatment regimens, the claims made for them, and evidence that supported these claims. In the final chapter the authors state,

> For none of the treatments reviewed in this report did the evidence support a finding of obvious, dramatic benefit that would obviate the need for formal evaluation to determine effectiveness, despite claims to that effect for a number of treatments.

For most physicians, this statement is sufficient: claims of efficacy are not supported by the facts. The report acknowledges that the general public, particularly those with cancer or who know someone with cancer, may not be satisfied with this conclusion, for many have heard of miraculous cures or prolonging of life when cancer patients use these alternative therapies. The report suggested that formal mechanisms for the rigorous clinical assessment of such claims might be developed. Implied is the belief that good clinical studies could favorably influence the public who, on seeing scientific evidence, would seek only proven and effective therapies. The problems entailed in starting such studies, the ethical considerations of entering patients in clinical trials of this type, and the effect of published results on patients' behavior were not extensively probed. I provide here a perspective on these problems.

As background, it is important to know about the ongoing Cancer Drug Development Program inaugurated by the National Cancer Institute in 1955.[2] By the early 1980s this rigorous and scientifically sound review process had been used to screen nearly three quarters of a million potentially active agents, including chemical synthetics, products of fermentation, plant derivatives, marine animal products, and biologic response modifiers.[2] Each of the agents tested held some hope when review began, yet fewer than 70 made it to market. It is likely there are few if any effective cancer chemotherapeutic drugs among the discarded hopefuls. Logistics dictate that only a fraction of these drugs could be put to a clinical test; thus, the filtering process is specifically designed to enhance the probability that agents entered into clinical trials are worthy of being tested for efficacy and have a reasonable chance of demonstrating a useful response.

The 1962 amendment to our food and drug laws, passed unanimously by Congress, required not only that drugs be safe but that they also be proved effective. Since its passage, some 6,800 drugs have been removed from drugstore shelves and 2,000 others have had their labels modified.[3] These laws represent some of our most important consumer protection assurances. Without them, our pharmacies would be stocked with worthless nostrums and the public would be at the mercy of drug entrepreneurs who might successfully convince the public, pharmacists, and physicians of a particular product's supposed effectiveness.

Perhaps unwittingly, the Office of Technology Assessment report, by encouraging the circumvention of the National Cancer Institute's carefully constructed drug development program, has invited the testing in humans of drugs not proved to be safe or to hold any reasonable hope of clinical activity. The OTA proposes the use of the "best case series" approach for selecting regimens for clinical trials. Practitioners using unconventional treatments would summarize their "best cases" and offer these as background data for a comparative clinical study of their method and that of orthodox medicine. This approach has never been documented as being a sound basis for selecting new agents for clinical trials and relies to a great extent on hearsay, sketchy medical records, and poorly documented responses. Drugs administered to patients now require approval of the Food and Drug Administration or the assignment of an investigational new drug number from the appropriate federal or state agency; this requires extensive supporting documentation based on solid science. It would be unwise to introduce into human subject research agents other than those that have gone through this evaluation.

Institutional review boards, charged with the responsibility of overseeing human subject research, must approve all clinical investigations, and here, too, is a problem. These review bodies are concerned with the true risk-benefit ratio of each study. Such evidence is derived from real data. To rely on hearsay is unacceptable, and to initiate a study testing a new treatment of a devastating disease with data based on unsubstantiated evidence would be unethical. Under current conditions, it is not possible to see how an institutional review board could approve a study testing the efficacy of a therapy that lacks a rationale for its effectiveness. Devoid of evidence of benefit and with unknown toxicity, the potential risk to patients would exceed the benefit and therefore could not be approved.

About the same time the Office of Technology Assessment published its report, Cassileth and colleagues compared the results of a study using carefully matched patients with advanced cancer, half of whom were treated at a clinic in San Diego, California, that administered unconventional therapy and half at a large university medical center.[4]

Cassileth was not only the senior author on this paper but served as a member of the advisory panel on unconventional

(Lewis JP: Clinical studies with make-believe drugs. West J Med 1992 Dec; 157:677-678)

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cancer treatments during the development of the OTA's report. The Cassileth study addressed two questions: Is the length of survival among terminal cancer patients treated at an unorthodox cancer clinic similar to the survival time of comparable patients cared for at a large medical facility? and Is the quality of life similar for patients cared for at both sites? Unfortunately, only the answer to the former question appears in the abstract's conclusion (survival is comparable); one needs to read the entire report carefully to uncover the answer to the second, which is, "Nevertheless, this study refutes the assumption that unproved therapies necessarily enhance the quality of life."[4]

Frontiers in medicine advance on a foundation of well-designed scientific studies. Unfortunately, those who advocate unproven remedies do not take their lead from science and thus are not influenced by the scientific method, including the results published by Cassileth and co-workers. In the concluding paragraph, the authors suggest they have demonstrated the feasibility of conducting investigations with unproven cancer remedies, and, in agreement with the OTA's study of the problem, the authors endorse the concept of ethical medicine joining with practitioners of unproven methods to test their regimens. Unfortunately, completing and publishing such studies does not close the door on the continued use of these worthless agents. Following the study by Moertel and associates on vitamin C, where no benefit was found, vitamin C did not suddenly cease to be advocated as effective therapy for cancer.[5] After Moertel and co-workers reported that no benefit was found but toxicity was documented, the use of amygdalin (Laetrile) persisted, although its use was declining at the time the study was published.[6] It is doubtful that their study was the cause of the demise of this toxic nostrum.

A more responsible approach to addressing the problem of unproven therapies is to inform the public more fully that well-trained physicians can do much to improve the quality of life of terminally ill patients and that there are some in society who offer themselves as health care practitioners, yet cannot point to peer-reviewed works to support their therapeutic response claims. For some reason society appears more willing to accept health care fraud than most other types of misleading business activities. This educational process requires a long-term commitment. In the meantime cancer quackery will remain a lucrative business.[1]

Clinical studies with unproven drugs, some of which are make-believe agents, cannot be carried out in the context of proper informed consent and should not become a part of our clinical drug development program seeking new and effective oncologic agents. What the OTA proposes is the use of an unscientific method, the "best case series" to investigate an unscientific therapy. As medical professionals, we must be cautious about setting up "scientific" studies of unproven agents when the outcome is going to have the appearance of endorsing unethical treatments and will have little or no effect on the use of unapproved and fraudulent therapies. History documents that carefully executed clinical studies with unconventional therapies do show lack of efficacy, but that these findings have no effect on the continued use of worthless remedies by those who profit from their distribution.

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Editorials

Orthostatic Hypotension in Earthlings and Space Travelers

HUMANITY'S first victory over the encumbrance of gravity occurred when humans evolved the capacity to maintain an upright posture. This capability was made possible by a major shift in the dominant function of the sympathetic nervous system. In the lower animals, the sympathetic nervous system had certainly been an important regulator of the circulation, but its most critical function was to mediate the "fight or flight" phenomenon. With the development of the upright posture, the sympathetic nervous system assumed a new burden, one that entailed a fundamental transformation of function. Henceforth, it would be inextricably linked to standing upright. In the comfortable life of modern humans, more norepinephrine is synthesized and released each day to maintain the upright posture than for any other purpose.

Humanity's second victory over gravity came with space travel, but it was only a partial victory. Of the many early concerns about the effects of weightlessness on human health, only a few have proved to be genuinely problematic. Orthostatic hypotension on return to Earth is operationally one of the most important of these. Although it resolves within days of returning to gravity, it can be a serious problem during shuttle reentry when gravitational force in a head-to-toe direction is transiently greater than 1*g*; loss of consciousness could occur under such circumstances, with serious consequences.

Orthostatic hypotension occurs when autonomic nervous system control over the heart and vasculature is overwhelmed or becomes dysfunctional.[1] In this issue of the journal, Alan S. Hollister, MD, PhD, provides a valuable guide to the many clinical causes of orthostatic hypotension.[2] Several points need to be kept in mind by physicians examining patients with symptoms that might be caused by orthostatic hypotension.

First, the diagnosis requires clinical vigilance and a willingness to take the extra time to obtain a blood pressure in the standing position as well as the supine or seated position. Because many patients with the Bradbury-Eggleston syndrome and the Shy-Drager syndrome have supine hypertension,[3] the erroneous—and, for these patients, dangerous—misdiagnosis of essential hypertension may be made. Obviously these patients will be harmed if they are given antihypertensive agents.

Second, the vasodepressor effect of food[4] can be used to help in diagnosing orthostatic hypotension; the diagnosis may be missed unless supine and upright blood pressures are measured in the hour following a high-carbohydrate meal. Before meals, many affected patients may not have a demonstrable fall in pressure with standing.

Third, medications are still the most common cause of symptomatic orthostatic hypotension.[3] The most insidious offender is amitriptyline, but many less commonly used tricyclic antidepressant agents have this effect. They are insidious because the orthostatic hypotension may not be noted in the first few days of therapy and therefore may not be recognized by the patient or physician as the actual cause of the clinical problem.

Finally, orthostatic hypotension is not synonymous with autonomic failure.[5] In an earlier era, adrenal failure was the most commonly recognized cause of orthostatic hypotension, and in the pivotal initial clinical description of autonomic failure, the critical issue of making this differential point occupied much of the attention of Bradbury and Eggleston.[6] Adrenal failure is a comparatively rare cause of orthostatic hypotension today. In mastocytosis, the mitral valve prolapse syndrome, and astronauts returning from space, however, it is unlikely that autonomic degeneration plays any actual role.[7]

The diversity of causes of orthostatic hypotension makes the physician's task difficult, but not impossible. By applying the approaches outlined by Hollister, the cause of most patients' orthostatic hypotension can be determined. Correct diagnosis often is the key to successful treatment.

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Has Our 'Healthy' Life-style Generated Eating Disorders?

AS ELLEN HALLER, MD, points out in her timely review article in this issue of the journal,[1] our young women, particularly those from reasonably well-to-do white families, have found themselves in the midst of an epidemic of eating disorders. In these patients we witness the collision of the cultural pressures on women, psychological vulnerabilities, and biologic factors that contribute to psychopathology and ill health. Research has documented social pressures on today's women to be thinner and to exercise more than was the standard in the 1940s and 1950s.[2] Although some attention to these matters is good, as with many other things, too much is not. As a result, surveys repeatedly show that about three quarters of women whose weights are fully in the normal range feel too fat and wish to lose weight; indeed, some studies have shown that they desire on average to weigh only slightly more than the weights in the anorexia nervosa range.[3] In only 1% to 3% do clinically significant anorexia nervosa and bulimia nervosa, develop, however. We do not understand why this small but far from insignificant subgroup has overt eating disorders, but current evidence suggests that anorexia nervosa or bulimia nervosa is more likely to develop in women with premorbid personalities and temperaments who tend to be particularly timid and avoidant, obsessional, or sensitive and moody and that women who have a greater tendency to be overweight may be more prone to have bulimia

nervosa. Furthermore, those at higher risk are more likely to come from homes in which weight preoccupation, family dysfunctional patterns, parents or siblings who tease about weight and appearance, substance abuse, and mood disorders are found. High rates of concurrent psychiatric disorders are found among patients with eating disorders, particularly mood, anxiety, obsessive-compulsive, substance abuse, and personality disorders.[4] The undernutrition and hunger resulting from self-starvation contribute to the appearance of many of the "psychological" symptoms of eating disorders such as food preoccupation, irritability, moodiness, obsessionality, compulsivity, and eating binges.

Regardless of the confluence of causes, once these disorders exist they are far from trivial: the morbidity and even mortality of anorexia nervosa are considerable, and this condition tends to have a long-term course with considerable ongoing psychological, social, and physical debility. And, whereas bulimia nervosa appears to be highly treatable, especially if caught early and when the common psychiatric comorbid conditions are concomitantly addressed, untreated patients are likely to remain ill for years.

Pediatricians, adolescent medicine specialists, physicians working with student health, sports medicine, and dance populations, gynecologists, gastroenterologists, and dentists are likely to see patients for whom preventive practices are indicated and patients with early, subclinical forms of these disorders. For example, a high percentage of women who present for infertility workups are underweight and have undetected eating disorders.[5] Given the high prevalence of eating disorders in these populations, a high index of suspicion for eating disorders is warranted. Physicians or their staffs, including nurse practitioners and registered dieticians, should educate patients regarding expected weight changes with menarche, appropriate weights for frame, healthy nutrition, and the importance of maintaining normal menstruation to prevent osteoporosis. When physicians are aware that young girls have been raised in "high pressure" households, they should seek opportunities to explicitly discuss these issues with the parents as well. Physicians are well served to review their personal attitudes toward weight and exercise. Those physicians who are overzealous regarding fat-free bodies, dieting, and constant exercise and who charismatically transmit these values to patients may unintentionally harm the insecure, compulsive young women they see by provoking iatrogenically induced eating disorder habits and preoccupations.

Multidisciplinary teams consisting of primary care physicians, registered dieticians, and psychiatrists or psychologists familiar with the treatment of eating disorders are the best approach to treatment. Hospital treatment is often needed for seriously malnourished patients and for those with psychological and behavioral disturbances that cannot be managed on an outpatient basis. Personal and family counseling and sensitive psychotherapy (including a cognitive-behavioral approach) are indicated in virtually every patient. Because psychopharmacologic agents such as fluoxetine and other antidepressant medications seem useful in many patients with bulimia nervosa and anorexia nervosa, a consultation with a psychiatrist familiar with the use of these agents for these conditions seems indicated where possible.[6-9] The American Psychiatric Association has just completed a set of practice guidelines for the treatment of eating disorders that should be of considerable use.[10]

Unfortunately, patients with severe eating disorders requiring hospital care are not well served by today's insurance climate. Too often available benefits fall far short of the actual clinical need, and evidence is mounting that patients who are discharged from hospital before achieving adequate weight gain and symptom remission are far more likely to suffer recurrences and to have chronic illness. As with other conditions, patients treated by experienced and well-qualified staffs may have better results than those treated in settings where such patients are rare.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Whooping Cough in Infancy

To the Editor: Pertussis is a serious illness in the young, in terms of both morbidity and mortality: 50% of cases and 70% of deaths occur in infancy.[1,2] We describe a case of pertussis in infancy, highlighting its atypical clinical features and briefly summarizing diagnosis and treatment.

Report of a Case

The patient, a 6-week-old child, was brought to the clinic with the report that she had turned blue. She was the product of a full-term pregnancy. None of the other six children in the family were currently ill. Although other children in the community had persistent coughs, none had been diagnosed with pertussis. This child had not yet received her first immunizations.

The patient's mother described illness for about three days. Notable symptoms were episodes of extreme dyspnea accompanied by cyanosis. These spells were characterized by a small amount of cough, described by the mother as slightly tight but not croupy. This was followed by the child's face turning dark blue, almost black, with accompanying mild cyanosis of hands and feet. The spells had been occurring for about 48 hours. The previous night two spells were characterized by prolonged cyanosis and apnea, such that the mother had done mouth-to-mouth breathing. She brought the child to the clinic the next morning.

On examination, the child was healthy appearing, well nourished, and cheerful. She smiled in response, babbled, and was taking a bottle. Temperature was 37°C (99°F). Her respirations were 20 per minute, and her pulse was 86 beats per minute. The physical examination revealed no abnormalities. She was having no respiratory distress. Her lungs were clear to auscultation without any audible wheezing or prolongation of expiration. She did not cough while in the clinic. Her leukocyte count in the clinic was 14×10^9 per liter (14,000 per μl), and the hematocrit was 0.55 (55%).

On the basis of the mother's reliability and the severity of the described symptoms, the child was admitted to the hospital for evaluation. In the emergency department while awaiting blood work and a room assignment, the child had another apneic spell, characterized by simple apnea with nearly no cough. Bradycardia with a rate of 30 was noted along with severe cyanosis. Positive pressure bag-assisted respiration was begun. She recovered spontaneous respirations in about two minutes. Her condition was otherwise unchanged.

Laboratory studies in the hospital showed a leukocyte count of 18×10^9 per liter with 0.73 lymphocytes. Electrolytes, blood urea nitrogen, glucose, and creatinine values were all normal. Her chest x-ray film showed mild perihilar infiltrates, interpreted as compatible with viral pneumonia.

She was admitted to the pediatric intensive care unit, where she had as many as 30 episodes daily of apnea, bradycardia to a rate of 30, with desaturation of her blood oxygen to 0.75 to 0.80 (75% to 80%). The spells would last as long as two minutes and were treated with simple blow-by oxygen. A nasogastric feeding tube was placed because of difficulty maintaining good oral intake. Her leukocyte count decreased to 13×10^9 per liter over the first week. Culture of a nasopharyngeal swab was positive for *Bordetella pertussis*. Studies for respiratory syncytial virus and chlamydia were negative. Erythromycin therapy was begun orally on admission, and she completed ten days of therapy.

She was treated in the intensive care unit for 18 days, with slow improvement in the severity and duration of her apneic spells. She was readmitted two days after release with an increased number of apneic spells and cyanosis and spent 8 more days in hospital. A regimen of albuterol was started after hyperinflation was noted on a repeat chest radiograph, and she was also given intravenous hydrocortisone sodium succinate, 10 mg per kg of body weight. After 24 hours she was switched to oral prednisolone, 15 mg every six hours. She was discharged to home on a tapered course of prednisolone. She had relapses at home of her apnea, cough, and cyanosis on two successive occasions when attempts were made to discontinue her oral prednisolone. After a 30-day slowly tapered course of prednisolone, she was able to tolerate stoppage without flares of her symptoms. Six months later, she is doing well.

Discussion. Pertussis is one of the most highly communicable diseases known, with reported attack rates of as high as 100%.[3] The highest mortality is in the young. Diagnosis in adults may be delayed or missed, and adults previously immunized may serve as a silent source of infection in the general community.[3]

Diagnosis of the disease is sometimes difficult. A positive culture is diagnostic, but false-negative cultures are common. The direct immunofluorescent test of nasopharyngeal secretions requires experienced personnel to interpret it accurately. Absolute lymphocytosis is a common and supportive finding, but is nonspecific. A fourfold rise in pertussis agglutinin titer is diagnostic but has poor sensitivity.

Neonatal pertussis appears to be a distinct clinical syndrome when compared with the classical descriptions of whooping cough. In infants the catarrhal stage has been noted to be absent, as it was in our patient. The paroxysmal stage in this patient had almost no cough, being characterized instead by apnea and choking with pronounced bradycardia. Other authors have reported similar findings in infants.[4,5] The convalescent stage in this case was prolonged.

Despite notable bradycardia and cyanosis, the apneic episodes in our patient were brief—1 to 2 minutes—and responded to blow-by oxygen and intravenous fluid maintenance. This appears to be the preferred treatment when possible. Treatment with antibiotics early in the catarrhal stage may shorten the course, but in most cases, eradication of the organism plays no role in the clinical course of the disease, other than shortening the period of communicability.[6,7]

Whether or not steroids have a beneficial role to play in the treatment of pertussis is an unanswered question.

Despite the availability of effective vaccines, whooping cough continues to be a problem because of inadequate levels of immunization. This is due to controversy over possible side effects from the vaccine. The Committee on Infectious Diseases of the American Academy of Pediatrics recently concluded that pertussis vaccine has not proved to be a cause of brain damage.[8]

Recently the Food and Drug Administration approved diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) to be used only as the fourth and fifth booster doses for children who have been immunized against diphtheria, tetanus, and pertussis with three doses of whole-cell DTP vaccine as their initial series.[9]

The current immunization schedule in the United States using whole-cell vaccine beginning at 2 months of age and acellular vaccine as boosters provides practical protection against pertussis but does not provide lifelong immunity. Prevention is still the best treatment, and immunization is the best prevention available.

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Crohn's Disease—A Rare Disorder in American Indians

To the Editor: The incidence of Crohn's disease in American Indians is exceedingly rare and usually uncomplicated.[1] Free perforation occurs in less than 1% of all patients with Crohn's disease.[2] We report a case of Crohn's disease with small bowel perforation in an American Indian.

Report of a Case

The patient, a 33-year-old Navajo man, had a three-hour history of abdominal pain. When seen, he was in severe distress with a rigid, quiescent, distended abdomen. A stool specimen was guaiac-positive. The rest of a physical examination revealed no abnormalities.

The patient had a history of chronic diarrhea and alcohol abuse, including toxic ingestions of Pine Sol, ethylene glycol, and hair spray.

Laboratory studies elicited the following values: hemoglobin, 68 grams per liter (6.8 grams per dl); hematocrit, 0.23 (23%); mean corpuscular volume, 60 fl (60 cu μm); mean corpuscular hemoglobin, 178 grams per liter (17.8 grams per dl); leukocyte count, 5×10^9 per liter (5,000 per μl); amylase, 40 U per liter; and urinalysis normal. An upright chest x-ray film showed pneumoperitoneum and no evidence of tuberculosis.

An exploratory laparotomy was done. There was mild peritonitis with 500 ml of cloudy fluid in the peritoneal cavity. There were skip lesions of fibrotic stenosis in the distal ileum. The intervening bowel was notably distended. A small perforation was located in an area of distended ileum. The mesentery of the involved ileum had pronounced lymphadenopathy and characteristic "creeping fat." The segment of gross disease encompassing 52 cm of ileum was resected, and a primary anastomosis was done.

Pathologic examination of the specimen showed submucosal edema, multiple shallow longitudinal ulcers, segments with chronic transmural inflammatory cell infiltrates, and dense fibrosis involving the entire bowel wall. No granulomas or abscesses were identified. The lesion was consistent with inflammatory bowel disease of the small bowel. Tissue cultures were negative for acid-fast bacilli, and a purified protein derivative (PPD) test was negative.

The patient was discharged on postoperative day 12 and continues to do well.

Comment

The Gallup (New Mexico) Indian Medical Center is a main referral center for the Navajo, Hopi, and Zuni tribes comprising about 190,000 people. Enteritis is commonly of an infectious cause in this population, due to tuberculosis or salmonella.[1] Primary infection with *Mycobacterium tuberculosis* results from drinking milk infected with the bovine strain and is seen in only 10% of patients. The rest have a secondary infection due to active pulmonary tuberculosis. Only 50% of patients with tuberculous enteritis will have active pulmonary tuberculosis, and 45% may have a negative PPD test. Thus, distinguishing Crohn's disease from tuberculous enteritis can be difficult in this population.

Tandon and Prakash, in reviewing the histologic features of intestinal tuberculosis and its distinction from Crohn's disease, stated that the diagnosis can usually be made without difficulty on microscopic evaluation.[3] In this patient, the submucosal edema, lack of granulomas, and transmural inflammatory cell infiltrates together with negative cultures and the absence of any clinical signs of tuberculosis led to the diagnosis of Crohn's disease. We do not know what effect the patient's previous toxic ingestions may have had on his current illness. Physicians treating American Indians should consider Crohn's disease in patients with suggestive symptoms.

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State AIDS Drug Program Expansion

To the Editor: I wish to tell your readers of the recent expansion of the AIDS [acquired immunodeficiency syndrome] Drug Program by the California Department of Health Services, Office of AIDS. This program, funded through a combination of state and federal funds, provides drugs for persons with the human immunodeficiency virus (HIV) who have no means to pay. Newly added drugs as of April 1, 1992, are ketoconazole, clotrimazole, and fluconazole. These are antifungal drugs that combat opportunistic infections associated with HIV disease. Fluconazole is also used to treat *Cryptococcus neoformans*.

Other drugs included in the program are zidovudine (AZT), aerosolized pentamidine, sulfadiazine, the combination of sulfamethoxazole and trimethoprim (Bactrim), pyrimethamine, didanosine (dideoxyinosine, DDI), dapsone, nystatin, ganciclovir, and clindamycin. The Office of AIDS has provided algorithms for all drugs covered by the program to assist physicians in determining the appropriate therapeutic regimen for their patients. The algorithms were developed through the review and assistance of physicians familiar with HIV disease. They may be used as a guide for treatment and may be obtained from the Office of AIDS by writing or calling our office.

To be eligible for the AIDS Drug Program, a person must meet these criteria:

- Have a valid prescription from a California-licensed physician,
- Have an annual adjusted gross income below $50,000, and
- Not be covered under Medi-Cal or a third-party insurance company.

The only exception is if a patient's private health insurance does not cover drugs as a benefit. Funds from the AIDS Drug Program may be used to cover the costs of an insurance copayment if an enrollee meets all other eligibility criteria.

Eligible persons who do not have full health coverage and whose annual adjusted gross income is between $27,240 and $50,000 have a copayment obligation based on their state income tax liability. Those with an adjusted gross income below $27,240 will receive the drug free of charge if they are without full health coverage.

For more information about the program, the eligibility requirements, or copies of the program guidelines and drug algorithms, please write to Richard Rockwell, State Department of Health Services, Office of AIDS, PO Box 942732, Sacramento, CA 94234-7320, or call (916) 323-4324.

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Cross-cultural Communication

To the Editor: The September 1992 issue of the journal on cross-cultural medicine was of interest to me. During the 31 years that I have run the Pediatric Cardiac Clinic at San Francisco General Hospital, I have watched the children of the world who had heart problems come before me. As more and more children with diverse ethnic backgrounds sought medical care at the clinic, I realized I had to do something about communication. I used translators whenever possible, but I was frustrated by my inability to give information about the children's heart problems to the families in a form that they could take home and discuss with the extended family.

About the same time, I noted that many medical students and graduate physicians whom I encountered were of widely disparate backgrounds and had language skills in areas where I was deficient—everything but English and Spanish. I began to encourage them to translate for me the "heart information sheets" that I had prepared in English and Spanish about such defects as atrial septal defect, ventricular septal defect, and tetralogy of Fallot so that the families could understand the ramifications of each defect.

I am pleased that the Pediatric Cardiac Clinic now is prepared to tell a family everything they want to know about, for example, transposition of the great arteries in nine languages: English, Spanish, Chinese, Japanese, Portuguese, Russian, Tagalog, Vietnamese, and German. I am currently working on Arabic and Hebrew.

With only 126 languages to go, including Urdu and Sanskrit, I will be prepared to welcome children with heart defects from any part of the globe!

Pediatric cardiologists who are interested in obtaining the material should contact me, and I will be glad to send it along.

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A Friendship Bridge to Vietnam

To the Editor: Friendship Bridge is a non-profit, humanitarian organization that is helping to fill the health care void that now exists in Vietnam. This tragic and poverty-stricken country has a barely functioning medical care system. Many of its hospitals offer little more than beds to patients, despite the presence of dedicated physicians and other health care professionals. Simply stated, Vietnam's medical community lacks everything, from the most basic supplies and equipment to additional training for its professionals.

Friendship Bridge works with physicians and hospitals in Vietnam (not with the Vietnamese government) in these ways: we send teams of American volunteer physicians and other health care professionals there for two-week periods to lecture and train their Vietnamese counterparts; we send new and used medical equipment and supplies to hospitals and clinics; and we seek sponsors who can underwrite visits to the United States by Vietnamese health care workers for up to three months of training.

Generally, our health care teams do not practice clinical medicine because we would rather train and teach Vietnamese physicians to do the necessary procedures. Here are some of the things we have accomplished in the few years that Friendship Bridge has been in existence:

- Twenty separate delegations have traveled to Vietnam to assess needs and have also hand-carried requested medical supplies.
- Since July 1990, over 100 tons of medical equipment, supplies, and books have been shipped to Vietnam to be distributed to six teaching hospitals in Saigon and Hanoi.
- We have sponsored 12 distinguished Vietnamese physicians, nurses, and dentists for advanced study in the Denver area.

• We have created teaching projects in nursing education, English training for Vietnamese physicians and nurses, cardiology, urology, orthopedics, respiratory therapy, physical therapy, critical care anesthesia, and dentistry.

We would welcome hearing from physicians and other health care professionals who wish to volunteer with us in some capacity. The need is so great in Vietnam that every discipline can find a role there. All of our volunteers pay their own expenses, which are usually tax-deductible. Friendship Bridge will make all the necessary arrangements, from forming the American teams (usually three or four professionals), to locating a specific hospital where you will teach, to arranging for your visa and reserving hotels. Spouses may accompany the volunteers and often serve as well, giving English lessons to Vietnamese citizens or using other skills they may have. Costs are approximately $2,500 to $3,000 per person, sums that are paid directly to airlines and hotels. Friendship Bridge does not charge a fee for its services, though contributions—tax deductible as allowed by law—are, of course, always appreciated.

For additional information you can contact me at Friendship Bridge, 33424 Deep Forest Rd, Evergreen, CO 80439; telephone (303) 421-1203; FAX (303) 423-7329.

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Lessons From the Practice

The Man Who Would Not Die

C. GRESHAM BAYNE, MD, *San Diego, California*

It started 15 years ago when I attempted to take a cyst from Captain Bobczynski's left earlobe. I was a second-year surgery resident, he a retired Navy captain famous for firing the torpedo spread that sank the Japanese ship *Shinano* during World War II. After the war, our families lived next door to each other during my childhood but separated when the patriarchs, both Navy captains, were reassigned. Now we were thrown together again by one of the mysterious quirks of fate so common in the Navy and in medicine.

It seemed reasonable to drop by his house and exercise my mediocre surgical talents and poor judgment, attempting to remove the cyst as the Captain sat stoically at his kitchen table. As a more mature surgeon might have anticipated, the cyst ruptured and the wound became infected. I made daily house calls to pack the wound and assuage my guilt for good intentions gone awry.

Over the next five years, the Captain developed a number of serious medical problems, born of a life at sea, nourished by cigarettes, and dictated by unfortunate genetic markers. His house was on my way home from work, and it became natural to drop by and manage these problems. On one of these calls, I asked him if his chest pain was any different in its nature or frequency. I had been controlling his angina with the usual drugs. He said, "No," but his wife, always parsimonious with words, contributed, "That's not true, honey, it is now waking you up at night!" Two weeks later the Captain had a four-vessel bypass for unstable angina.

He began a difficult recovery in the hospital, marked by a profound depression that even his family could not penetrate. Armed with family support, he elected to return home despite severe residual lung damage, heart failure, and wound pain. Again I was challenged with repeated house calls whose function seemed to be more observation than therapy. I found myself quoting Sir William Osler, the Father of Medicine: "The purpose of the physician is to amuse the patient while nature effects the cure."

Over the next ten years, the Captain developed one serious medical problem after another. He suffered transient ischemic attacks, recurrent infarctions requiring a pacemaker, and renal failure requiring dialysis. During these episodes, I continually marveled at the strength of the Captain's faith.

Several months ago an extraordinary event occurred. Because of outside interests I was spending less time in hospitals but had, for the first time in about two years, exchanged duties with a partner and was working in the hospital emergency department. About ten minutes after entering the hospital I heard the awful alarm followed by "Code Blue, Code Blue, 4 west, room 423." I ran to the room to find the staff working on an elderly dialysis patient who had been found dead sitting in his chair. The patient was now completely blue—a long time without a heartbeat or oxygen. As I removed the therapist's mask to begin intubation, I recognized the Captain. He was in the hospital to revise yet another complication in the shunt used for his dialysis. Just as I told all to stop the procedures, that his living will was well known to me, and he did not desire heroic measures, the nurse shouted, "All clear," and shocked his heart back to life. His pacemaker was working; his blood pressure was normal; he was comatose, and, by all criteria, brain dead. I called his wife who thanked me for "being there." After cautioning her to return to the hospital, I went back to the room to listen to his labored respirations despite positioning and suction. The Captain and I had discussed such matters before, and I knew that he would want to take his last breaths without obstruction if possible. I began to intubate him only to find that the cause of the arrest was a huge piece of luncheon veal wedged in his throat.

I thought my actions had delayed any chance he had for survival and had condemned him to the remainder of life in a vegetative state. There are few things that can shake a veteran of nearly two decades in a major trauma center, but this did. I left orders for his wife to see me as soon as she arrived and went to the emergency department. Thirty minutes later, a nurse brought incredible news. The Captain was sitting up and asking, for the first time in a year, to be taken to dialysis. After my shift, I went to his room and confessed what had happened. He looked at me with vague interest and said, "Remarkable, isn't it?"

Last month the Captain stopped his dialysis. His hulking frame had been reduced to a shell that had to be carried from bed to commode and back. He spoke little but understood everything. I went to see him at home to arrange for contingency plans to prepare for the inevitable. I found myself kneeling beside his bed, babbling about the role he had played in my life, what he had taught me. I had learned how not to tell patients what was best for them, but to inform them of the choices and the likely risks and results of procedures. I had learned how to make true house calls using all pieces of the environment in which patients lived and dealt with their condition. I had learned the wonderful feeling of respect and trust that family doctors in years past must have known. Perhaps most important, I began to appreciate how powerful a force my counsel could be, given that respect and trust, and to know how weak it really was when compared to the trust and faith this devout man found in his God.

The Captain died in his sleep several days later, a smile on his face, leaving a legacy of trust and belief that today gives

(Bayne CG: The man who would not die. West J Med 1992 Dec; 157:685-686)

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the lie to so much of our materialistic grasping. This man, this strong man, who had sent the largest warship ever built to a watery grave, left a wife and seven children with extraordinary talents and convinced a bevy of doctors that there is still a mandate for loving care for our patients.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

DEAR JOHN LETTER TO MY UTERUS

Dear Uterus,

We've not been formally introduced.
Oh, well.

Who wants to meet a lover at a funeral?

Old cozy blanket, fuzzy mitten, coffee pot

simmering behind my stomach wall,
out of sight,

like my cousins in Oklahoma
like my pink angora sweater

misshapen in a trunk.
I've been happy knowing you're there.

Thank-you for cooking up my children.
I forgive you for letting one slip by.

But, lately you've become a nuisance,

like a dog who won't quit licking,
a too precocious child,

a lingering houseguest.
Like a sailor on leave,
you're a creature of excess.

I won't spell it out.
You know what you've been doing.

There, I feel better, this clears the air.
Must close, so long now, job well done,

all things considered, it's been fun.

DONNA HILBERT©
Cerritos, California

TELL ME, DOCTOR

What will the test determine?
Winds wash all my houses.
What will the lab report?

The girl preparing the slide
Has sculptured eyes.
Her cheekbones are not human.

I am transparent, except
For aquamarine paper.
I display myself.

I am not alarmed.
You are precisely pleasant,
As I had hoped.

There is a polar sun
Where I have spread my legs.
I have come iced for you.

Tell me the truth.
Your files are locked.
Here I am all my sins.

Make me a speech.
Let me rain unrecorded.
Bill me for bucketing.

Soon I'll be safe.
The truth is negative.
You tell me so.

The rain retreats.
My powers return.
I become a name you speak.

Now I am visible.
Ready to lose.
Your girl ghosts by.

ROSE MARY PROSEN©
Cleveland, Ohio

Volume 157

INDEX

July-December 1992

AUTHOR INDEX

Abbott, Joseph A., San Francisco, Calif (Nov) 592
Aboulafia, David M., Seattle, Wash (Dec) 672
Adelman, Raymond D., Norfolk, Va (Nov) 554
Adornato, Bruce T., Palo Alto, Calif (Oct) 471
Ai, Everett, San Francisco, Calif (Jul) 67
Allen, Wain, Kaman, Utah (Dec) 681
Amundson, Dennis E., San Diego, Calif (Aug) 197
Anton, Bette, Berkeley, Calif (Dec) 637
Armstrong, Robert W., Los Gatos, Calif (Aug) 182
Arnold, Anthony C., Los Angeles, Calif (Oct) 451
Arvin, Ann M., Stanford, Calif (Nov) 587
Auerback, Marvin L., Foster City, Calif (Jul) 87, (Dec) 683
Ault, Mark J., Los Angeles, Calif (Jul) 65

Babb, Richard R., Palo Alto, Calif (Oct) 444
Badri, Maher, San Bernardino, Calif (Oct) 455
Balamuniswamy, Geetha, Chicago, Ill (Nov) 573
Balazs, Mary, Lexington, Va (Jul) 40
Balmes, John R., San Francisco, Calif (Aug) 169
Barker, Judith C., San Francisco, Calif (Sep) 248
Barnhart, Scott, Seattle, Wash (Oct) 425
Bayne, C. Gresham, San Diego, Calif (Dec) 685
Behrman, Richard E., Stanford, Calif (Jul) 74
Bennett, Charles L., Durham, NC (Jul) 41
Bernstein, Michael S., San Francisco, Calif (Aug) 169
Beyene, Yewoubdar, San Francisco, Calif (Sep) 328
Biaggioni, Italo, Nashville, Tenn (Dec) 679
Biswas, Manoj K., New Orleans, La (Aug) 184
Blanchard, Daniel G., San Diego, Calif (Nov) 562
Boe, Marilyn J., Bloomington, Minn (Aug) 153
Bowser, Benjamin P., Hayward, Calif (Sep) 286
Brandstater, Murray E., Loma Linda, Calif (Dec) 666
Braun, Jonathan, Los Angeles, Calif (Aug) 158
Brigden, Malcolm L., Victoria, BC, Canada (Oct) 440
Brod, Meryl, San Francisco, Calif (Sep) 333
Brodkin, Carl A., Seattle, Wash (Oct) 425
Brown, Corwin, Santa Ana, Calif (Dec) 645
Brown, Scott E., Loma Linda, Calif (Dec) 666
Browner, Warren S., San Francisco, Calif (Nov) 534
Bulger, Roger J., Washington, DC (Aug) 186
Burgard, Renee, Stanford, Calif (Dec) 665

Call, Timothy B., San Diego, Calif (Aug) 197
Cardenas, Diana D., Seattle, Wash (Dec) 665
Carmack, Mary Ann, Stanford, Calif (Nov) 587
Carson, Robert I., Denver, Colo (Aug) 197
Carter, Lu, Norfolk, Neb (Jul) 82
Cassel, Christine K., Chicago, Ill (Aug) 191
Castorina, Joseph, Seattle, Wash (Oct) 425
Catania, Joseph, San Francisco, Calif (Jul) 32
Catanzarite, Val A., San Diego, Calif (Oct) 454
Chang, Helen, Los Angeles, Calif (Jul) 41
Charles, Gerald, San Francisco, Calif (Sep) 310
Charles, Sara C., Chicago, Ill (Oct) 433
Chester, Barbara, Tucson, Ariz (Sep) 301
Chin, Soo-Young, San Jose, Calif (Sep) 305
Chou, Tony, San Francisco, Calif (Nov) 544
Clark, William R., Indianapolis, Ind (Nov) 571
Clever, Linda Hawes, San Francisco, Calif (Sep) 247, (Nov) 584
Coates, Thomas, San Francisco, Calif (Jul) 32
Cody, Jim, San Antonio, Tex (Sep) 374
Cohen, Deborah A., New Orleans, La (Oct) 430
Congilosi, Susan M., Gallup, NM (Dec) 682
Conover, William A., Newport Beach, Calif (Jul) 79
Copeland, Helen M., Charlotte, NC (Nov) 530
Coren, Harry Z., San Francisco, Calif (Oct) 472
Cory, David, Los Angeles, Calif (Oct) 430
Cosentino, Anthony M., San Francisco, Calif (Aug) 170
Cousins, Larry M., San Diego, Calif (Oct) 454
Cozen, Harry J., Westlake Village, Calif (Oct) 471
Crawshaw, Ralph, Portland, Ore (Aug) 201

Daniell, William, Seattle, Wash (Oct) 425
Datz, Frederick L., Salt Lake City, Utah (Jul) 60
Davidson, Mayer B., Los Angeles, Calif (Aug) 199
Dawson, Jo Ann, Los Angeles, Calif (Jul) 41
Desmond, Brian, San Francisco, Calif (Sep) 323
Drasner, Kenneth, San Francisco, Calif (Nov) 564
DuChene, Alain G., Minneapolis, Minn (Nov) 534
Dudley, Denise F., Seattle, Wash (Oct) 452

Edlin, Brian R., Atlanta, Ga (Jul) 41
Engel, Mary, North Bergen, NJ (Oct) 439
Erslev, Allan J., Philadelphia, Pa (Aug) 195
Esselman, Peter C., Seattle, Wash (Dec) 665
Euler, Gary L., San Bernardino, Calif (Oct) 455

Faig, Jeffrey C., Stanford, Calif (Jul) 64
Feldman, David, Stanford, Calif (Jul) 64
Feldman, Jamie, Urbana, Ill (Sep) 345
Felton, Jean Spencer, Mendocino, Calif (Oct) 469
Feng, Timothy L., San Diego, Calif (Nov) 562
Filloux, Francis M., Salt Lake City, Utah (Aug) 179
Fitzgerald, Faith, Sacramento, Calif (Jul) 87, (Aug) 193
Fogarty, Carrie L., Garden Grove, Calif (Oct) 455
Foster, Erin, San Diego, Calif (Oct) 454
Frank, Barry S., Reno, Nev (Aug) 149
Frisch, Paul R., Portland, Ore (Oct) 433
Fullilove, Mindy Thompson, New York, NY (Jul) 32
Fullilove, Robert E. III, New York, NY (Jul) 32

Gaffney, F. Andrew, Nashville, Tenn (Dec) 679
Ganiats, Theodore G., La Jolla, Calif (Oct) 472
Gardner, John W., Stanford, Calif (Oct) 457
Garrett, Karen, Berkeley, Calif (Jul) 32
Gartrell, Nanette K., San Francisco, Calif (Aug) 139
Gates-Williams, Jan, San Francisco, Calif (Sep) 350
Geiderman, Joel, Los Angeles, Calif (Jul) 65
Geiman, Benjamin J., Seattle, Wash (Jul) 27, (Oct) 472
Gellert, George, Santa Ana, Calif (Oct) 455, (Dec) 645
Gelmont, David M., South Pasadena, Calif (Aug) 171
Gibbons, Robert D., Chicago, Ill (Oct) 433
Gilman, Stuart C., Long Beach, Calif (Sep) 310
Girsh, Faye J., San Diego, Calif (Aug) 188
Gold, Ellen B., Davis, Calif (Sep) 367
Gold, Steven J., Whittier, Calif (Sep) 290
Golden, Eve, San Francisco, Calif (Jul) 32
Goldstone, Robert L., Newport Beach (Jul) 88
Goldwater, Harland, Santa Barbara, Calif (Aug) 202
Goodson, William H. III, San Francisco, Calif (Aug) 139
Guglielmo, Joe, San Francisco, Calif (Aug) 174
Gutknecht, David R., Danville, Pa (Jul) 87

Haffner, Linda, Stanford, Calif (Sep) 255
Haller, Ellen, San Francisco, Calif (Dec) 658
Harmatz, Alexander, Stanford, Calif (Jul) 48
Hattner, Robert S., San Francisco, Calif (Jul) 62
Havens, Peter L., Milwaukee, Wis (Jul) 84
Hedeker, Donald, Chicago, Ill (Oct) 433
Herman, Doris L., Gallup, NM (Dec) 682
Heurtin-Roberts, Suzanne, San Francisco, Calif (Sep) 333
Heydorn, William H., San Francisco, Calif (Nov) 569
Heyer, Nicholas J., Seattle, Wash (Oct) 425
Hilbert, Donna, Cerritos, Calif (Dec) 686
Hindle, William H., Los Angeles, Calif (Aug) 152
Hobson, Mana, San Francisco, Calif (Nov) 539
Holland, Gary N., Los Angeles, Calif (Oct) 448
Hollister, Alan S., Denver, Colo (Dec) 652
Holtan, Neal, Minneapolis, Minn (Sep) 301
Hubbard, Rebecca, Seattle, Wash (Oct) 425
Hulley, Stephen, San Francisco, Calif (Jul) 32, (Nov) 534
Huston, James, Santa Ana, Calif (Dec) 645

Jackson, M. Njeri, Richmond, Va (Sep) 350
Jackson, Richard J., Berkeley, Calif (Dec) 648
Jackson, Stephen H., Monte Sereno, Calif (Nov) 567
Jacobs, Michael B., Stanford, Calif (Dec) 670
Jaffe, Kenneth M., Seattle, Wash (Dec) 664
Jenkins-Monroe, Valata, Alameda, Calif (Sep) 350
Jensen, Lloyd R., Salt Lake City, Utah (Dec) 641
Jonsen, Albert R., Seattle, Wash (Aug) 192
Justice, Judith, San Francisco, Calif (Sep) 310

Kahn, Norman B., Sacramento, Calif (Jul) 44
Kalinyak, Judith, San Francisco, Calif (Jul) 64
Katz, Mitchell H., San Francisco, Calif (Aug) 144
Kaufman, Joel D., Seattle, Wash (Oct) 425
Keates, Richard H., Irvine, Calif (Oct) 453
Kegeles, Susan, San Francisco, Calif (Jul) 32

Keifer, Matthew, Seattle, Wash (Oct) 425
Keller, Patricia A., Salt Lake City, Utah (Dec) 641
Kerlikowske, Karla M., San Francisco, Calif (Aug) 144
Kerr, Lynne, Salt Lake City, Utah (Aug) 179
Kinyoun, James L., Seattle, Wash (Nov) 530
Klessig, Jill, Los Angeles, Calif (Sep) 316
Koenig, Kristi L., San Francisco, Calif (Nov) 591
Kozarek, Richard A., Seattle, Wash (Jul) 83
Kramer, B. Josea, Los Angeles, Calif (Sep) 281

Lawrence, E. Clinton, Stanford, Calif (Aug) 173
Lazarus, Harrison M., Salt Lake City, Utah (Nov) 527
Lee, Philip R., San Francisco, Calif (Nov) 576
Leung, Jacqueline M., San Francisco, Calif (Nov) 565
Lew-Ting, Chin-Yin, Los Angeles, Calif (Sep) 337
Lewis, Jerry P., Sacramento, Calif (Dec) 677
Lifshin, Lyn, Niskayuna, NY (Sep) 344
Lipson, Juliene G., San Francisco, Calif (Sep) 271
Litt, Iris, New York, NY (Sep) 322
Lo, Bernard, San Francisco, Calif (Aug) 139
Longmore, Paul K., Stanford, Calif (Aug) 190
Lutrin, C. L., Sacramento, Calif (Jul) 61
Luttrull, Jeffrey K., Ventura, Calif (Oct) 449

McDonald, Craig M., Sacramento, Calif (Dec) 664
McDonnell, Peter J., Los Angeles, Calif (Oct) 449
McDougall, I. Ross, Stanford, Calif (Jul) 62
McKee, Ann C., Boston, Mass (Nov) 588
Maddix, Daniel S., San Francisco, Calif (Jul) 55
Mahoney, Cynthia A., Stanford, Calif (Dec) 670
Marcus, Robert, Stanford, Calif (Jul) 64
Marin, Barbara, San Francisco, Calif (Jul) 32
Markle, George B. IV, Carlsbad, NM (Nov) 592
Mason, Susan E., Seattle, Wash (Oct) 425
Massagli, Teresa L., Seattle, Wash (Dec) 664
Merkley, Kevin H., Irvine, Calif (Oct) 453
Merryman, Robert, Santa Ana, Calif (Dec) 645
Meyers, Hildy B., Santa Ana, Calif (Oct) 455
Mikhail, Maged S., Los Angeles, Calif (Nov) 566
Milliken, Nancy, San Francisco, Calif (Aug) 139
Mizock, Barry A., Chicago, Ill (Nov) 573
Mo, Bertha, San Francisco, Calif (Sep) 260
Mobed, Ketty, Davis, Calif (Sep) 367
Moncrief, William H., Jr, San Francisco, Calif (Nov) 569
Moore, Douglas F., Santa Ana, Calif (Oct) 455
Moore, Linda, New Orleans, La (Aug) 184
Morrison, Sherie L., Los Angeles, Calif (Aug) 158
Mull, Nathan H. San Diego, Calif (Aug) 197
Muller, Jessica H., San Francisco, Calif (Sep) 323
Myers, Martin G., Toronto, Ontario, Canada (Nov) 586

Nagaoka, Gail, Bellflower, Calif (Dec) 668
Nancarrow, Paul A., Oakland, Calif (Nov) 554
Nesbitt, Thomas S., Sacramento, Calif (Jul) 44
Ning, Theodore C., Jr, Evergreen, Colo (Dec) 683

Omidian, Patricia A., San Francisco, Calif (Sep) 271
Ong, Eddie, Bellflower, Calif (Dec) 668
Orcutt, James C., Seattle, Wash (Oct) 452

Padmanabhan, Krishnan, Brooklyn, NY (Dec) 675
Palerm, Juan Vicente, Santa Barbara, Calif (Sep) 362
Palevsky, Harold I., Stanford, Calif (Aug) 171
Parisi, Marguerite T., Los Angeles, Calif (Jul) 62
Petersen, Jeffrey, Stanford, Calif (Aug) 154
Peterson, John, San Francisco, Calif (Jul) 32
Petty, Thomas L., Denver, Colo (Oct) 463
Petz, Lawrence, Los Angeles, Calif (Dec) 668
Piacquadio, Daniel, San Diego, Calif (Jul) 87
Pinevich, Anthony J., Pittsburgh, Pa (Aug) 154
Pliskin, Karen L., San Francisco, Calif (Sep) 295
Pollack, Murray M., Washington, DC (Aug) 149
Portera, S. G., New Orleans, La (Aug) 184
Prendergast, Thomas J., San Bernardino, Calif (Oct) 455, (Dec) 648
Presley, Robert W., Los Gatos, Calif (Nov) 564
Pritikin, Jonathan, Stanford, Calif (Jul) 48
Prosen, Rose Mary, Cleveland, Ohio (Dec) 686
Pyskoty, Charlene E., Chicago, Ill (Oct) 433

Raffin, Thomas A., Stanford, Calif (Aug) 171
Ralls, John, Santa Ana, Calif (Dec) 645
Ramakrishna, Jayashree, Bangalore, India (Sep) 265
Reiter, Thomas, Neptune, NJ (Jul) 78
Rizk, Norman W., Stanford, Calif (Aug) 173
Robertson, David, Nashville, Tenn (Dec) 679
Robertson, Richard, Bellflower, Calif (Dec) 668
Robertson, William O., Seattle, Wash (Jul) 74
Robinette, Pam, San Diego, Calif (Oct) 454
Rosendale, Douglas E., Gallup, NM (Dec) 682
Rosenstock, Linda, Seattle, Wash (Oct) 425
Rubio, Pedro, Houston, Tex (Nov) 591
Rutherford, George W., Sacramento, Calif (Oct) 471

Sacpharn, Kaota, San Pablo, Calif (Sep) 310
Salpeter, Shelley, San Jose, Calif (Oct) 421
Sauseda, Wayne E., Sacramento, Calif (Dec) 683
Saxon, Andrew, Los Angeles, Calif (Aug) 158
Schenker, Marc B., Davis, Calif (Sep) 367
Scherger, Joseph E., Sacramento, Calif (Jul) 44
Schneider, Jack M., San Diego, Calif (Oct) 454
Schoen, Edgar J., Oakland, Calif (Oct) 470
Schultz, Carl H., Orange, Calif (Nov) 591
Scribner, Richard, Los Angeles, Calif (Oct) 430
Senter, Phyllis J., Santa Rosa, Calif (Oct) 469
Sessler, Daniel I., San Francisco, Calif (Nov) 566
Shafer, Steven L., Palo Alto, Calif (Nov) 563
Shapiro, Bertrand J., Los Angeles, Calif (Aug) 174
Shapiro, Joseph I., Denver, Colo (Aug) 197
Sharma, Om P., Los Angeles, Calif (Aug) 172
Shlian, Deborah, Los Angeles, Calif (Jul) 41
Siegel, David, San Francisco, Calif (Jul) 32
Singha, Navneet K., Chicago, Ill (Oct) 433
Slagle, Alan, Sacramento, Calif (Dec) 648
Smith, Arnold L., Seattle, Wash (Jul) 27, (Oct) 472
Sokas, Rosemary K., Washington, DC (Oct) 460
Soll, Andrew H., Los Angeles, Calif (Oct) 465
Sommer, Alfred, Baltimore, Md (Jul) 71
Speizer, Frank E., Boston, Mass (Nov) 585
Stamatoyannopoulos, John A., Seattle, Wash (Dec) 631
Starnes, Vaughn A., Stanford, Calif (Aug) 173
Stein, Myron, Los Angeles, Calif (Aug) 175
Stevens, Wendell C., Portland, Ore (Nov) 563
Steward, David J., Los Angeles, Calif (Nov) 567
Stiehm, E. Richard, Los Angeles, Calif (Dec) 668
Stover, Bert, Seattle, Wash (Oct) 425
Styrt, Barbara, East Lansing, Mich (Oct) 461
Summers, Paul R., Salt Lake City, Utah (Aug) 184
Sutherland, Anne, St Paul, Minn (Sep) 276

Tanji, Jeffrey L., Sacramento, Calif (Jul) 44
Tawney, Suresh, Las Vegas, Nev (Aug) 177
Teraoka, Jeffrey, Stanford, Calif (Dec) 665
Thangathurai, Duraiyah, Los Angeles, Calif (Nov) 566
Theodore, James, Stanford, Calif (Aug) 173
Thiemann, Sue, San Francisco, Calif (Aug) 139
Thurman, David J., Salt Lake City, Utah (Dec) 641
Tornambe, Paul E., La Jolla, Calif (Oct) 450
Tran, Vinh Tan, Los Angeles, Calif (Oct) 451
Tremper, Kevin K., Ann Arbor, Mich (Oct) 471
Trible, Waring R., San Diego, Calif (Aug) 197
Tse, Victor, Palo Alto, Calif (Oct) 471
Tsuchiya, Naoyuki, Tokyo, Japan (Aug) 133
Tucker, Harvey J., San Francisco, Calif (Dec) 637
Tucker, Kelly J., San Francisco, Calif (Dec) 637

Uomoto, Jay M., Seattle, Wash (Dec) 665

Varon, Joseph, Stanford, Calif (Dec) 670
Velji, Anvar, Sacramento, Calif (Jul) 84
Vora, Sharad, Brooklyn, NY (Dec) 675

Wall, Randolph, Los Angeles, Calif (Aug) 158
Wallace, Steven P., Los Angeles, Calif (Sep) 337
Waller, Kirsten, Berkeley, Calif (Dec) 648
Walsh, Judith M. E., San Francisco, Calif (Oct) 469
Waltman, Richard E., Tacoma, Wash (Oct) 474
Warner, Laurel, San Francisco, Calif (Jul) 55
Waxman, Alan D., Los Angeles, Calif (Jul) 60
Webb, James P., Garden Grove, Calif (Oct) 455
Weinman, David, Stanford, Calif (Jul) 48
Weiss, Mitchell G., Boston, Mass (Sep) 265
Wiener-Kronish, Jeanine P., San Francisco, Calif (Aug) 174
Wiley, James, Berkeley, Calif (Jul) 32
Williams, Adrian J., Los Angeles, Calif (Aug) 175
Williams, Landon R., Berkeley, Calif (Sep) 350
Williams, Ralph C., Jr, Gainesville, Fla (Aug) 133
Williams, Scott D., Salt Lake City, Utah (Dec) 641

Wilson, Archie F., Orange, Calif (Aug) 174
Wilson, Bruce E., Las Vegas, Nev (Aug) 177
Wong, Victor K., Bellflower, Calif (Dec) 668
Wray, Linda A., Los Angeles, Calif (Sep) 357

Yager, Joel, Los Angeles, Calif (Dec) 679
Yarnell, Stanley K., San Francisco, Calif (Dec) 663
Young, Harvey, Stanford, Calif (Jul) 48

Zamber, Ronald W., Seattle, Wash (Nov) 530
Zelikovic, Israel, Seattle, Wash (Nov) 554

IN MEMORIAM

California Medical Association:

Abraham, Samuel V., Feb 20, 1992 (Aug) 125
Agcaoili, Felix, Feb 10, 1992 (Jul) 20
Anderson, Gerald J., May 1992 (Aug) 125
Bacci, Orval J., Apr 24, 1992 (Jul) 20
Bagnall, William Stanley, Feb 9, 1992 (Nov) 516
Blinn, John F., Jr, Jun 21, 1992 (Aug) 125
Boscoe, Anthony R., Oct 12, 1992 (Dec) 618
Bouillon, Victor J., Aug 24, 1992 (Nov) 516
Boyle, Joseph F., Jul 16, 1992 (Nov) 516
Bradshaw, Stanley P., May 30, 1992 (Nov) 516
Bush, Robert C., Mar 18, 1992 (Jul) 20
Cady, Carl F., Feb 22, 1992 (Nov) 516
Canfield, Merritt C., Sep 27, 1992 (Dec) 618
Cannon, Thomas P., May 1992 (Aug) 125
Carson, Joseph P., Aug 17, 1992 (Nov) 516
Chatton, Milton J., Feb 17, 1992 (Jul) 20
Christman, Albert H., Jul 22, 1992 (Nov) 516
Clark, Richard N., Feb 26, 1992 (Nov) 516
Cochran, Frederick B., Jr, Feb 1992 (Jul) 20
Collins, John Austin, Sep 1992 (Dec) 618
Compton, Alfred D., Jr, Jul 10, 1992 (Nov) 516
Cotler, Gerald, May 31, 1992 (Nov) 516
Cronin, Daniel J., Oct 21, 1992 (Dec) 618
Curtis, Robert H., Oct 3, 1992 (Dec) 618
Cyr, Gerald A., Jul 5, 1992 (Nov) 516
David, Charles B., Mar 25, 1992 (Jul) 20
Delavega, Frederick J., Jul 8, 1992 (Dec) 618
Dillon, Victor M., Oct 18, 1992 (Dec) 618
Dinwiddie, Robert C., Sep 17, 1992 (Dec) 618
Dyar, Robert, Jul 25, 1992 (Nov) 516
Ekegren, James K., Oct 6, 1992 (Dec) 618
Fischer, Golda, Aug 6, 1992 (Dec) 618
Fish, Albert, Jul 1992 (Nov) 516
Flood, Anthony J., Jr, Jul 11, 1992 (Nov) 516
Frank, Dee E., Feb 28, 1992 (Nov) 516
Gallaher, John A., Jun 20, 1992 (Dec) 618
Gallion, Charles S., Apr 19, 1992 (Jul) 20
Gardiner, Theodore D., May 29, 1992 (Dec) 618
Gerlach, Karl D., Apr 1992 (Aug) 125
Gibbings, Raymond J., Aug 12, 1992 (Dec) 618
Ginsberg, Julius E., Feb 8, 1992 (Jul) 20
Gray, Harold F., Jr, Jun 8, 1992 (Nov) 516
Grief, Marvin H., Sep 28, 1992 (Dec) 618
Griffin, Richard G., Apr 1992 (Nov) 516
Hagan, Donald D., Mar 7, 1992 (Jul) 20
Hannon, Joseph L., Aug 6, 1992 (Nov) 516
Harrington, Eileen S., Feb 13, 1992 (Nov) 516
Harris, Jerome S., Jul 31, 1992 (Nov) 516
Haruff, John J., Apr 29, 1992 (Jul) 20
Hudson, Heber S., Mar 22, 1992 (Jul) 20
Iseri, Lloyd T., Feb 22, 1992 (Jul) 20
Katz, Hyman M., Aug 8, 1992 (Dec) 618
Kaveney, Robert E., Jun 8, 1992 (Aug) 125
Kershnar, Harvey E., Jun 12, 1992 (Nov) 516
Klotz, Norman, May 25, 1992 (Nov) 516
Knobloch, Joseph D., Jul 28, 1992 (Nov) 516
Krause, Hazel W., Feb 8, 1992 (Nov) 516
Lammel, Harry G., Oct 26, 1992 (Dec) 618
Lange, Otto H., Jan 13, 1992 (Nov) 516
Lawther, Harry C., Mar 31, 1992 (Jul) 20
Lubeck, Benjamin B., Apr 18, 1992 (Jul) 20
Lusignan, Harry, May 7, 1992 (Aug) 125
Madison, Mitchell, Sep 9, 1992 (Dec) 618
Mayhew, Stephen H., Mar 1992 (Jul) 20
Mitchell, Cyril L., Aug 8, 1992 (Nov) 516
Mitchell, James E., Sep 21, 1992 (Dec) 618
Morrison, Norman D., Jr, Aug 27, 1992 (Dec) 618
Morton, Mortimer E., Mar 1992 (Jul) 20
Nies, Arthur J., Jul 20, 1992 (Nov) 516
Noble, James H., Mar 10, 1992 (Jul) 20
Nogle, Charles, Jr, Feb 18, 1992 (Jul) 20
Northam, Allan Leslie, Jul 5, 1992 (Nov) 516
O'Donnell, Bernard Vincent, Sep 12, 1992 (Dec) 618
Pascoe, Richard L., Feb 16, 1992 (Jul) 20
Passoff, Todd L., May 8, 1992 (Nov) 516
Peoples, Stuart A., Feb 14, 1992 (Jul) 20
Peterson, Robert H., Mar 18, 1992 (Jul) 20
Philips, Irving, Aug 29, 1992 (Dec) 618
Pont, Maynard E., Mar 26, 1992 (Aug) 125
Poska, Ted A., Mar 2, 1992 (Jul) 20
Ransom, Dow H., Jr, Jul 17, 1992 (Nov) 517
Robb, Robert C., Mar 29, 1992 (Aug) 125
Rosenberg, Benjamin B., Aug 12, 1992 (Dec) 618
Rosenberg, Joel M., Jun 1992 (Aug) 125
Rumsey, John M., Jun 19, 1992 (Nov) 517
Rush, Norman J., Feb 16, 1992 (Dec) 618
Savage, Philip M., Jr, Mar 12, 1992 (Jul) 20
Schmutz, Melvin A., Jun 9, 1992 (Aug) 125
Schunke, Gustave B., Feb 20, 1992 (Jul) 20
Seavers, Ray, Jr, Jul 30, 1992 (Nov) 517
Sibul, Ebba Kuldvere, May 21, 1992 (Dec) 618
Smith, Lowell R., Aug 27, 1992 (Dec) 618
Smitter, Robert C., Oct 26, 1992 (Dec) 618
Spratt, Robert J., Sep 27, 1992 (Dec) 618
Stansbury, John R., Feb 23, 1992 (Jul) 20
Steele, Ashby, May 1, 1992 (Aug) 125
Steiner, Paul, Apr 8, 1992 (Nov) 517
Steiss, Charles F., Apr 27, 1992 (Dec) 618
Swartout, Roy III, Aug 2, 1992 (Dec) 618
Teague, Conrad B., Mar 29, 1992 (Jul) 20
Thompson, William H., Aug 9, 1992 (Dec) 618
Turner, Joseph E., May 1992 (Aug) 125
Vasko, John R., Sep 1, 1992 (Dec) 619
Wapnick, Anthony A., Sep 14, 1992 (Dec) 619
Watson, Frances R., Apr 4, 1992 (Aug) 125
Watt, James Y., Jul 21, 1992 (Nov) 517
Weinberger, Herbert, Jan 1992 (Jul) 20
Weizer, Ernest A., Mar 21, 1992 (Jul) 20
Williams, James A., Jul 21, 1992 (Dec) 619
Wilson, William M., Mar 27, 1992 (Jul) 20
Wynia, Frederick, Feb 29, 1992 (Jul) 20
Zeff, Maurice, Feb 21, 1992 (Nov) 517

Idaho Medical Association:

Lesser, Louis F., Oct 21, 1992 (Dec) 619

New Mexico Medical Society:

Albrecht, Philip, Sep 4, 1992 (Dec) 619
Badger, William E., Mar 12, 1992 (Jul) 20
Coleman, Tobert C., May 26, 1992 (Nov) 517
Farris, Lee L., May 29, 1992 (Aug) 125
Hudson, Heber Scott, Mar 22, 1992 (Aug) 125
Kempers, Bert, Oct 24, 1992 (Dec) 619
Kosicki, Zigmund W., Sep 13, 1992 (Dec) 619
McKinnon, Daniel A., Aug 24, 1992 (Nov) 517
Rhodes, Gustave G., Mar 24, 1992 (Jul) 20
Service, Allen C., Jan 1992 (Aug) 125
Sleeper, Donald C., Apr 3, 1992 (Aug) 125
Vergara, Luataro G., Apr 3, 1992 (Jul) 20
Waldman, Milton, Mar 31, 1992 (Jul) 20
Wilkinson, Lawrence, Aug 9, 1992 (Dec) 619

SUBJECT INDEX

A

Abdominal Aorta and Cholecystectomy—A Peer Review Organization Perspective, see *Simultaneous Reconstruction of the*
Abdominal Aortic Aneurysm—Incidence in a Hospital Population at Risk, Harrison M. Lazarus (Nov) 527
Abortion, see *Let's Not Do With Euthanasia What We Did With*
Academic Health Centers, see *'R' Word—'Rationing' of Health Care and the Role of*
Academically Affiliated Occupational and Environmental Medicine Clinic, see *10-Year Experience of an*
Acid-Base Disorders Revisited (Correspondence), Robert I. Carson, Joseph I. Shapiro (Aug) 197
Response, Richard J. Haber (Aug) 197
Acquired Immunodeficiency Syndrome, see *Pseudothrombocytopenia in a Child With*

Adult Still's Disease Presenting as Fever of Undetermined Origin in a Patient With Leukemoid Reaction, Barry A. Mizock, Geetha Balamuniswamy . . . (Nov) 573
Adult Varicella in the United States Navy 1984–1987, see *Manifestations of*
African-American Culture and AIDS Prevention—From Barrier to Ally (Cross-cultural Medicine—A Decade Later—Special Issue), Benjamin P. Bowser . . . (Sep) 286
African-American Infant Mortality, see *Business of Preventing*
AIDS, see *French are Different*
AIDS Drug Program Expansion, see *State*
AIDS in Multiethnic Neighborhoods in San Francisco, California—The Population-Based AMEN Study, see *Risk for*
AIDS Prevention, see *African-American Culture and*
AIDS-Related Pulmonary Infection, see *Thin-Walled Lung Cavities and Cysts Secondary to*
AMEN Study, see *Risk for Acquired Immunodeficiency Syndrome in Multiethnic Neighborhoods in San Francisco, California—The Population-Based*
American Indians, see *Crohn's Disease—A Rare Disorder in*
American Indians, see *Health and Aging of Urban*
Anemia, see *Recombinant Erythropoietin Therapy in Renal and Non-Renal*
Anesthesiology, see *Epitomes*
Aneurysm—Incidence in a Hospital Population at Risk, see *Abdominal Aortic*
Anion Gap in Hyperglycemia, see *Reflections on*
Another Health Food Hazard—γ-Hydroxybutyrate-induced Seizures (Correspondence), Bruce T. Adornato, Victor Tse . . . (Oct) 471
Antibody, see *Second Century of*
Anti-inflammatory Drugs, see *Gastrointestinal Complications of Nonsteroidal*
Aortic Aneurysm—Incidence in a Hospital Population at Risk, see *Abdominal*
Asplenia and Hyposplenism—Persistent Uncertainties, see *Complications of*
Assisted Suicide—What Euthanasia Activists Say, What People With Disabilities Say (Editorial Comment), Paul K. Longmore . . (Aug) 190

B

Bacterial Meningitis—A Meta-analysis of Randomized Controlled Trials, see *Dexamethasone and*
Beyond Words (Cross-cultural Medicine—A Decade Later—Special Issue), Linda Hawes Clever . . . (Sep) 247

Biomedical Science:

Future Prospects for Treatment of Hemoglobinopathies, John A. Stamatoyannopoulos . . . (Dec) 631
Molecular Mimicry—Hypothesis or Reality?, Naoyuki Tsuchiya, Ralph C. Williams, Jr . . . (Aug) 133

Blood-Saturated Operating-Room Shoe Covers, Paul R. Summers, Manoj K. Biswas, S. G. Portera, Linda Moore . . . (Aug) 184
Correspondence, Pedro A. Rubio . . . (Nov) 591
Borrelia burgdorferi From Ticks in Southern California, see *Isolation of*
Brain After the Rapid Development of Hypernatremia, see *Diffuse Demyelinating Lesions of*
Breast Cancer, see *Carcinocythemia—A Terminal Manifestation of Metastatic*
Breast Health in Chinese-American Women, see *Modesty, Sexuality, and*
Business of Preventing African-American Infant Mortality (Cross-cultural Medicine—A Decade Later—Special Issue), Jan Gates-Williams, M. Njeri Jackson, Valata Jenkins-Monroe, Landon R. Williams . . . (Sep) 350

C

Caffeine, Coffee, and the Medical Consequences, see *Wake Up and Smell the Coffee*
California, see *Exaggerated Threat of Childhood Lead Poisoning in*
California, see *Licensing of Tissue Banks in*
California Student Health Service, see *Health Care Use by Human Immunodeficiency Virus-Infected Students at a*
Cancer Screening in Women (Correspondence), Phyllis J. Senter . . . (Oct) 469
Response, Judith M. E. Walsh . . . (Oct) 469
Carcinocythemia—A Terminal Manifestation of Metastatic Breast Cancer, David M. Aboulafia . . . (Dec) 672
Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism, see *Chronic Atypical Seizure Disorder and*
Central Nervous System Disease, see *Long-standing Latent Idiopathic Hypoparathyroidism Discovered During Concurrent*
Cerebral Infarction as a Remote Complication of Childhood *Haemophilus influenzae* Meningitis, Lynne Kerr, Francis M. Filloux . . . (Aug) 179
Cesarean Section Incision During Labor at Home, see *Maternal Death Due to Rupture of a Low Transverse*
Chemoprophylaxis, see *Tuberculosis*
Chest Diseases, see *Epitomes*
Child Health, see *Scientific Medicine, Social Ills, and*
Child With the Acquired Immunodeficiency Syndrome, see *Pseudothrombocytopenia in a*
Childhood Lead Poisoning in California, see *Exaggerated Threat of*
Children, see *Urinary Tract Infections in*
Children Younger Than 5 Years in Urban Utah, see *Submersion Injuries in*
Chinese-American Women, see *Modesty, Sexuality, and Breast Health in*
Chinese Example, see *Ethical Dilemmas in a Cross-cultural Context*
Cholecystectomy—A Peer Review Organization Perspective, see *Simultaneous Reconstruction of the Abdominal Aorta and*
Chronic Atypical Seizure Disorder and Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism, Jeffrey C. Faig, Judith Kalinyak, Robert Marcus, David Feldman . . . (Jul) 64
Clinical Note—Doctor-Patient Bonding (Lessons From the Practice), Ralph Crawshaw . . . (Aug) 201
Clinical Studies With Make-believe Drugs (Commentary), Jerry P. Lewis . . . (Dec) 677
Coffee, and the Medical Consequences, see *Wake Up and Smell the Coffee—Caffeine,*

Commentary:

Clinical Studies With Make-believe Drugs, Jerry P. Lewis . . . (Dec) 677
Earthquakes and the Office-Based Surgeon, William A. Conover . . . (Jul) 79
Correspondence, Carl H. Schultz, Kristi L. Koenig . . . (Nov) 591
Global Health Leadership—A Continuing US Challenge, Alfred Sommer . . . (Jul) 71
Editorial, Anvar Velji . . . (Jul) 84
Personal Renewal, John W. Gardner . . . (Oct) 457
Physician Aid in Dying—What Doctors Say, What Patients Say, Faye J. Girsh . . . (Aug) 188
Editorial Comments, Paul K. Longmore, Christine K. Cassel, Albert R. Jonsen, Faith Fitzgerald . . . (Aug) 190
Playing the Cost-Containment Game, William O. Robertson . . (Jul) 74
'R' Word—'Rationing' of Health Care and the Role of Academic Health Centers, Roger J. Bulger . . . (Aug) 186
Scientific Medicine, Social Ills, and Child Health, Richard E. Behrman . . . (Jul) 74

Community Hospital Pediatric Intensive Care Unit, see *Quantitative Quality Assurance in a*
Complications of Asplenia and Hyposplenism—Persistent Uncertainties (Editorial), Barbara Styrt . . . (Oct) 461

Conferences and Reviews:

Do We Need an Intravenous Fluoroquinolone?, Daniel S. Maddix, Laurel Warner . . . (Jul) 55
Eating Disorders—A Review and Update, Ellen Haller . . . (Dec) 658
Editorial, Joel Yager . . . (Dec) 679
Endoscopic Laser Therapy in Gastroenterology, Jonathan Pritikin, David Weinman, Alexander Harmatz, Harvey Young . . . (Jul) 48
Editorial, Richard A. Kozarek . . . (Jul) 83
Erythropoietin Therapy in Patients With Chronic Renal Failure, Anthony J. Pinevich, Jeffrey Petersen . . . (Aug) 154
Editorial, Allan J. Erslev . . . (Aug) 195
Gastrointestinal Complications of Nonsteroidal Anti-inflammatory Drugs, Richard R. Babb . . . (Oct) 444
Editorial, Andrew H. Soll . . . (Oct) 465

Orthostatic Hypotension—Causes, Evaluation, and Management, Alan S. Hollister . . . (Dec) 652
Editorial, David Robertson, F. Andrew Gaffney . . . (Dec) 679
Overwhelming Postsplenectomy Infection—Still a Problem, Malcolm L. Brigden . . . (Oct) 440
Editorial, Barbara Styrt . . . (Oct) 461
Second Century of the Antibody—Molecular Perspectives in Regulation, Pathophysiology, and Therapeutic Applications, Moderator: Jonathan Braun; Discussants: Andrew Saxon, Randolph Wall, Sherie L. Morrison . . . (Aug) 158
Urinary Tract Infections in Children—An Update, Israel Zelikovic, Raymond D. Adelman, Paul A. Nancarrow . . . (Nov) 554
Editorial, Mary Ann Carmack, Ann M. Arvin . . . (Nov) 587
Wake Up and Smell the Coffee—Caffeine, Coffee, and the Medical Consequences, Tony Chou . . . (Nov) 554
Editorial, Martin G. Myers . . . (Nov) 586

Controlling a Syphilis Epidemic, Deborah A. Cohen, Richard Scribner, David Cory . . . (Oct) 430

Correspondence:

Acid-Base Disorders Revisited, Robert I. Carson, Joseph I. Shapiro . . . (Aug) 197
Response, Richard J. Haber . . . (Aug) 197
Another Health Food Hazard—γ-Hydroxybutyrate-induced Seizures, Bruce T. Adornato, Victor Tse . . . (Oct) 471
Blood-Saturated Shoe Covers, Pedro A. Rubio . . . (Nov) 591
Cancer Screening in Women, Phyllis J. Senter . . . (Oct) 469
Response, Judith M. E. Walsh . . . (Oct) 469
Correction, Daniel Piacquadio . . . (Jul) 87
Crohn's Disease—A Rare Disorder in American Indians, Susan M. Congilosi, Douglas E. Rosendale, Doris L. Herman . . . (Dec) 682
Cross-cultural Communication, Marvin L. Auerback . . . (Dec) 683
Discounting Our Future, Harry Z. Coren . . . (Oct) 472
Response, Theodore G. Ganiats . . . (Oct) 472
Earthquakes and the Practicing Physician, Carl H. Schultz, Kristi L. Koenig . . . (Nov) 591
Exaggerated Threat of Childhood Lead Poisoning in California—Epidemic by Edict, Edgar J. Schoen . . . (Oct) 470
A Friendship Bridge to Vietnam, Theodore C. Ning, Jr . . . (Dec) 683
History and Diagnosis, Faith Fitzgerald . . . (Jul) 87
David R. Gutknecht . . . (Jul) 87
If Syncope, Think Long QT, Marvin L. Auerback . . . (Jul) 87
Let's Not Do With Euthanasia What We Did With Abortion, George B. Markle IV . . . (Nov) 592
Licensing of Tissue Banks in California, George W. Rutherford . . . (Oct) 471
Manifestations of Adult Varicella in the United States Navy 1984-1987, Nathan H. Mull, Dennis E. Amundson, Waring R. Trible, Timothy B. Call . . . (Aug) 197
Meta-analyses Revisited, Benjamin J. Geiman, Arnold L. Smith . . . (Oct) 472
Pulse Oximeter Versus Electrocardiogram, Harry J. Cozen . . . (Oct) 471
Response, Kevin K. Tremper . . . (Oct) 471
Put Your Money Where Your Advice Is, Joseph A. Abbott . . . (Nov) 592
State AIDS Drug Program Expansion, Wayne E. Sauseda . . . (Dec) 683
Successful Treatment of Markedly Symptomatic Patients With Type II Diabetes Mellitus Using High Doses of Sulfonylurea Agents, Mayer B. Davidson . . . (Aug) 199
'What Kind of Work Do You Do?,' Jean Spencer Felton . . . (Oct) 469
Whooping Cough in Infancy, Wain Allen, Cynthia Campbell Barnes . . . (Dec) 681

Cost-Containment Game, see *Playing the*
Costs and Coverage—Pressures Toward Health Care Reform (Special Series), Philip R. Lee . . . (Nov) 576
Editorial . . . (Nov) 584
Crohn's Disease—A Rare Disorder in American Indians (Correspondence), Susan M. Congilosi, Douglas E. Rosendale, Doris L. Herman . . . (Dec) 682
Cross-cultural Communication (Correspondence), Marvin L. Auerback . . . (Dec) 683

Cross-cultural Medicine—A Decade Later—Special Issue:

Beyond Words, Linda Hawes Clever . . . (Sep) 247
Cultural Diversity—Changing the Context of Medical Practice, Judith C. Barker . . . (Sep) 248
Translation is Not Enough—Interpreting in a Medical Setting, Linda Haffner . . . (Sep) 255
Modesty, Sexuality, and Breast Health in Chinese-American Women, Bertha Mo . . . (Sep) 260
Health, Illness, and Immigration—East Indians in the United States, Jayashree Ramakrishna, Mitchell G. Weiss . . . (Sep) 265
Health Issues of Afghan Refugees in California, Juliene G. Lipson, Patricia A. Omidian . . . (Sep) 271
Gypsies and Health Care, Anne Sutherland . . . (Sep) 276
Health and Aging of Urban American Indians, B. Josea Kramer . . . (Sep) 281
African-American Culture and AIDS Prevention—From Barrier to Ally, Benjamin P. Bowser . . . (Sep) 286
Mental Health and Illness in Vietnamese Refugees, Steven J. Gold . . . (Sep) 290
Dysphoria and Somatization in Iranian Culture, Karen L. Pliskin . . . (Sep) 295
Working With Refugee Survivors of Torture, Barbara Chester, Neal Holtan . . . (Sep) 301
This, That, and The Other—Managing Illness in a First-Generation Korean-American Family, Soo-Young Chin . . . (Sep) 305
Use of Traditional and Modern Health Services by Laotian Refugees, Stuart C. Gilman, Judith Justice, Kaota Saepharn, Gerald Charles . . . (Sep) 310
Effect of Values and Cultures on Life-Support Decisions, Jill Klessig . . . (Sep) 316
Ethical Dilemmas in a Cross-cultural Context—A Chinese Example, Jessica H. Muller, Brian Desmond . . . (Sep) 323
Medical Disclosure and Refugees—Telling Bad News to Ethiopian Patients, Yewoubdar Beyene . . . (Sep) 328
Older Russian Emigrés and Medical Care, Meryl Brod, Suzanne Heurtin-Roberts . . . (Sep) 333
Getting By at Home—Community-Based Long-term Care of Latino Elders, Steven P. Wallace, Chin-Yin Lew-Ting . . . (Sep) 337
The French Are Different—French and American Medicine in the Context of AIDS, Jamie Feldman . . . (Sep) 345
Business of Preventing African-American Infant Mortality, Jan Gates-Williams, M. Njeri Jackson, Valata Jenkins-Monroe, Landon R. Williams . . . (Sep) 350
Health Policy and Ethnic Diversity in Older Americans—Dissonance or Harmony?, Linda A. Wray . . . (Sep) 357
Season in the Life of a Migrant Farm Worker in California, Juan Vicente Palerm . . . (Sep) 362
Occupational Health Problems Among Migrant and Seasonal Farm Workers, Ketty Mobed, Ellen B. Gold, Marc B. Schenker . (Sep) 367

Cultural Diversity—Changing the Context of Medical Practice (Cross-cultural Medicine—A Decade Later—Special Issue), Judith C. Barker . . . (Sep) 248
Current Management of Diabetic Retinopathy, Everett Ai . . . (Jul) 67
Cysts Secondary to AIDS-Related Pulmonary Infection, see *Thin-Walled Lung Cavities and*

D

Death, Politics, and Philosophy (Editorial Comment), Albert R. Jonsen . . . (Aug) 192
Dexamethasone and Bacterial Meningitis—A Meta-analysis of Randomized Controlled Trials, Benjamin J. Geiman, Arnold L. Smith . . . (Jul) 27
Editorial, Peter L. Havens . . . (Jul) 84
Correspondence, Benjamin J. Geiman, Arnold L. Smith . . (Oct) 472
Diabetes Mellitus, see *Successful Treatment of Markedly Symptomatic Patients With Type II . . . Using High Doses of Sulfonylurea Agents*
Diabetic Retinopathy, see *Current Management of*
Diagnosis, see *History and*
Diffuse Demyelinating Lesions of the Brain After the Rapid Development of Hypernatremia, William R. Clark . . . (Nov) 571
Editorial, Ann C. McKee . . . (Nov) 588
Discounting Our Future (Correspondence), Harry Z. Coren . . (Oct) 472
Response, Theodore G. Ganiats . . . (Oct) 472
Doctor-Patient Bonding, see *Clinical Note*
Do We Need an Intravenous Fluoroquinolone? (Conferences and Reviews), Daniel S. Maddix, Laurel Warner . . . (Jul) 55

[Drowning], see *Submersion Injuries in Children Younger Than 5 Years in Urban Utah*
Drugs, see *Clinical Studies With Make-believe*
Dysphoria and Somatization in Iranian Culture (Cross-cultural Medicine—A Decade Later—Special Issue), Karen L. Pliskin . . . . . (Sep) 295

E

Earthquakes and the Office-Based Surgeon (Commentary), William A. Conover . . . . . (Jul) 79
Correspondence, Carl H. Schultz, Kristi L. Koenig . . . . . (Nov) 591
East Indians in the United States, see *Health, Illness, and Immigration*
Eating Disorders—A Review and Update (Conferences and Reviews), Ellen Haller . . . . . (Dec) 658

Editorial Comment:

Assisted Suicide—What Euthanasia Activists Say, What People With Disabilities Say, Paul K. Longmore . . . . . (Aug) 190
Death, Politics, and Philosophy, Albert R. Jonsen . . . . . (Aug) 192
Physician Aid in Dying—Finding the Middle Ground, Faith Fitzgerald . . . . . (Aug) 193
Popular Movement for Physician-Assisted Dying—What the Public Is Saying, What Physicians Are Hearing, Christine K. Cassel . . . . . (Aug) 191

Editorials:

Caffeine Under Examination—A Passing Grade, Martin G. Myers . . . . . (Nov) 586
Complications of Asplenia and Hyposplenism—Persistent Uncertainties, Barbara Styrt . . . . . (Oct) 461
Eight Years and Counting—What Can Americans Do?, Anvar Velji . . . . . (Jul) 84
Getting Some Breathing Room—Persuading Patients to Stop Smoking, Frank E. Speizer . . . . . (Nov) 585
Has Our 'Healthy' Life-style Generated Eating Disorders?, Joel Yager . . . . . (Dec) 679
Health Care Reform—Another View . . . . . (Nov) 584
Meta-analysis Redux—Steroids and Meningitis Revisited, Peter L. Havens . . . . . (Jul) 84
Correspondence, Benjamin J. Geiman, Arnold L. Smith . . (Oct) 472
'New Habits of Mind'—Bridging the Gap Between Public Health and Clinical Medicine, Rosemary K. Sokas . . . . . (Oct) 460
Nonsteroidal Anti-inflammatory Drugs and Ulcers, Andrew H. Soll . . . . . (Oct) 465
Orthostatic Hypotension in Earthlings and Space Travelers, David Robertson, F. Andrew Gaffney, Italo Biaggioni . . . . (Dec) 679
Osmotic Shifts, Metabolic Compromise, and the Vulnerability of the Pons, Ann C. McKee . . . . . (Nov) 588
Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia, Allan J. Erslev . . . . . (Aug) 195
Treatment Strategies in the Prevention of Tuberculosis, Thomas L. Petty . . . . . (Oct) 463
Urinary Tract Infections—Navigating Complex Currents, Mary Ann Carmack, Ann M. Arvin . . . . . (Nov) 587
You Light Up My Life . . . and Liver—Gastroenterologic Laser Therapy in the 1990s, Richard A. Kozarek . . . . . (Jul) 83

Effect of Human Immunodeficiency Virus Infection on the Distribution and Outcome of Pneumonia in Intensive Care Units, Kelly J. Tucker, Bette Anton, Harvey J. Tucker . . . . . (Dec) 637
Effect of Values and Cultures on Life-Support Decisions (Cross-cultural Medicine—A Decade Later—Special Issue), Jill Klessig . . . . . (Sep) 316
Effects of the Multiple Risk Factor Intervention Trial Smoking Cessation Program on Pulmonary Function—A Randomized Controlled Trial, Warren S. Browner, Alain G. DuChene, Stephen B. Hulley . . . . . (Nov) 534
Editorial, Frank E. Speizer . . . . . (Nov) 585
Ehrlichiosis in a Visitor to Virginia, Robert W. Armstrong . . (Aug) 182
Eight Years and Counting—What Can Americans Do? (Editorial), Anvar Velji . . . . . (Jul) 84
[Elderly], see *Medications in Older Patients*
Electrocardiogram, see *Pulse Oximeter Versus*
Emigrés and Medical Care, see *Older Russian*
Endoscopic Laser Therapy in Gastroenterology (Conferences and Reviews), Jonathan Pritikin, David Weinman, Alexander Harmatz, Harvey Young . . . . . (Jul) 48
Editorial, Richard A. Kozarek . . . . . (Jul) 83
Endrin, see *Seizures After Eating a Snack Food Contaminated With the Pesticide*
Environmental Medicine Clinic, see *The 10-Year Experience of an Academically Affiliated Occupational and*

Epitomes:

Anesthesiology:

Transesophageal Echocardiography, Timothy L. Feng, Daniel G. Blanchard . . . . . (Nov) 562
New Applications of Propofol, Steven L. Shafer . . . . . (Nov) 562
'Do-Not-Resuscitate' Orders in Operating Rooms, Wendell C. Stevens . . . . . (Nov) 563
Novel Approaches to the Treatment of Neuropathic Pain, Robert W. Presley . . . . . (Nov) 564
Postoperative Pain, Kenneth Drasner . . . . . (Nov) 564
Perioperative Myocardial Ischemia, Jacqueline M. Leung . . . (Nov) 565
Sedating Patients in Intensive Care Units, Maged S. Mikhail, Duraiyah Thangathurai . . . . . (Nov) 566
Perioperative Temperature Control, Daniel I. Sessler . . . . . (Nov) 566
Postoperative Apnea Syndrome in Premature Infants, David J. Steward . . . . . (Nov) 567
Autologous Blood Transfusion Therapy . . . . . (Nov) 567

Chest Diseases:

Occupational Asthma, John R. Balmes . . . . . (Aug) 169
Antibiotics for Pneumonia, Michael S. Bernstein . . . . . (Aug) 169
Diagnosis of Pulmonary Embolism, Anthony M. Cosentino . . (Aug) 170
Thrombolytic Treatment of Pulmonary Embolism, Harold I. Palevsky, Thomas A. Raffin . . . . . (Aug) 171
Lung-Assist Devices, David M. Gelmont . . . . . (Aug) 171
Bronchiolitis Obliterans Organizing Pneumonia, Om P. Sharma . . . . . (Aug) 172
Advances in Pulmonary Biopsy Techniques, Norman W. Rizk . . . . . (Aug) 173
Lung Transplantation, E. Clinton Lawrence, James Theodore, Vaughn A. Starnes . . . . . (Aug) 173
Monoclonal Therapy for Bacteremia and Sepsis, Joe Guglielmo, Jeanine P. Wiener-Kronish . . . . . (Aug) 174
Conventional Treatment of Cystic Fibrosis, Bertrand J. Shapiro . . . . . (Aug) 174
Aerosolized Bronchodilators, Archie F. Wilson . . . . . (Aug) 174
Screening for Obstructive Sleep Apnea Using Pulse Oximetry, Adrian J. Williams, Myron Stein . . . . . (Aug) 175

Nuclear Medicine:

Use of Thallium 201 in Tumor Evaluation, Alan D. Waxman . (Jul) 60
Technetium 99m-Hexamethyl Propyleneamine Oxime-Labeled Leukocytes for Diagnosis of Infection, Frederick L. Datz . . (Jul) 60
Radionuclide Evaluation of Brain Death, C. L. Lutrin . . . . . (Jul) 61
Radionuclide Therapy for Thyroid Disease, I. Ross McDougall . . . . . (Jul) 62
Diagnostic and Therapeutic Uses of Metaiodobenzylguanidine, Marguerite T. Parisi, Robert S. Hattner . . . . . (Jul) 62

Ophthalmology:

Medical Treatment of Retinal Infections in Patients With AIDS, Gary N. Holland . . . . . (Oct) 448
Photorefractive Keratectomy, Peter J. McDonnell . . . . . (Oct) 449
Macular Surgery, Jeffrey K. Luttrull . . . . . (Oct) 449
Laser Treatment of Diabetic Retinopathy, Paul E. Tornambe . (Oct) 450
Retinitis Pigmentosa—New Advances in Ophthalmic Genetics, Vinh Tan Tran . . . . . (Oct) 451
Current Therapy for Disorders of the Optic Nerve, Anthony C. Arnold . . . . . (Oct) 451
Graves' Ophthalmopathy, Denise F. Dudley, James C. Orcutt . (Oct) 452
Small-Incision Cataract Operation, Richard H. Keates, Kevin H. Merkley . . . . . (Oct) 453

Physical Medicine and Rehabilitation:

Late Effects of Poliomyelitis—An Update on Fatigue and Weakness, Stanley K. Yarnell . . . . . (Dec) 663
Prophylaxis and Treatment of Posttraumatic Epilepsy With Phenytoin, Teresa L. Massagli . . . . . (Dec) 663

Neurobehavioral and Family Functioning Following Traumatic Brain Injury in Children, Craig M. McDonald, Kenneth M. Jaffe . . . . . (Dec) 664
Treatment of Postconcussion Syndrome, Jay M. Uomoto, Peter C. Esselman, Diana D. Cardenas . . . . . (Dec) 665
Family Support and Stroke Rehabilitation, Jeffrey Teraoka, Renee Burgard . . . . . (Dec) 665
Focal Dystonia in Musicians, Scott E. Brown . . . . . (Dec) 666
Venous Thromboembolism in Stroke, Murray E. Brandstater. (Dec) 666

Erythropoietin Therapy in Patients With Chronic Renal Failure (Conferences and Reviews), Anthony J. Pinevich, Jeffrey Petersen . . . . . (Aug) 154
Editorial, Allan J. Erslev . . . . . (Aug) 195
Ethical Dilemmas in a Cross-cultural Context—A Chinese Example (Cross-cultural Medicine—A Decade Later—Special Issue), Jessica H. Muller, Brian Desmond . . . . . (Sep) 323
Ethiopian Patients, see *Medical Disclosure and Refugees—Telling Bad News to*
Ethnic Diversity in Older Americans—Dissonance or Harmony?, see *Health Policy and*
Euthanasia, see *Let's Not Do With*
[Euthanasia], see *Physician Aid in Dying*
Exaggerated Threat of Childhood Lead Poisoning in California—Epidemic by Edict (Correspondence), Edgar J. Schoen . . . . . (Oct) 470

F

Factors Influencing Family Physicians to Continue Providing Obstetric Care, Thomas S. Nesbitt, Norman B. Kahn, Jeffrey L. Tanji, Joseph E. Scherger . . . . . (Jul) 44
Farm Workers, see *Occupational Health Problems Among Migrant and Seasonal*
Fever of Undetermined Origin in a Patient With Leukemoid Reaction, see *Adult Still's Disease Presenting as*
Fishers, see *Scombroid-Fish Poisoning—Underreporting and Prevention Among Non-Commercial Recreational*
Fluoroquinolone, see *Do We Need an Intravenous*
[Foodborne Disease], see *Scombroid-Fish Poisoning—Underreporting and Prevention Among Non-Commercial Recreational Fishers*
French Are Different—French and American Medicine in the Context of AIDS (Cross-cultural Medicine—A Decade Later—Special Issue), Jamie Feldman . . . . . (Sep) 345
A Friendship Bridge to Vietnam (Correspondence), Theodore C. Ning, Jr . . . . . (Dec) 683
Future Prospects for Treatment of Hemoglobinopathies (Biomedical Science), John A. Stamatoyannopoulos . . . . . (Dec) 631

G

γ-Hydroxybutyrate-induced Seizures, see *Another Health Food Hazard*
Gastroenterologic Laser Therapy in the 1990s, see *You Light Up My Life . . . and Liver*
Gastroenterology, see *Endoscopic Laser Therapy in*
Gastrointestinal Complications of Nonsteroidal Anti-inflammatory Drugs (Conferences and Reviews), Richard R. Babb . . . . . (Oct) 444
Editorial, Andrew H. Soll . . . . . (Oct) 465
Getting By at Home—Community-Based Long-term Care of Latino Elders, (Cross-cultural Medicine—A Decade Later—Special Issue), Steven P. Wallace, Chin-Yin Lew-Ting . . . . . (Sep) 337
Getting Some Breathing Room—Persuading Patients to Stop Smoking (Editorial), Frank E. Speizer . . . . . (Nov) 585
Global Health Leadership—A Continuing US Challenge (Commentary), Alfred Sommer . . . . . (Jul) 71
Editorial, Anvar Velji . . . . . (Jul) 84
Gypsies and Health Care (Cross-cultural Medicine—A Decade Later—Special Issue), Anne Sutherland . . . . . (Sep) 276

H

Haemophilus influenzae Meningitis, see *Cerebral Infarction as a Remote Complication of Childhood*
Has Our 'Healthy' Life-style Generated Eating Disorders? (Editorial), Joel Yager . . . . . (Dec) 679
Health, Illness, and Immigration—East Indians in the United States (Cross-cultural Medicine—A Decade Later—Special Issue), Jayashree Ramakrishna, Mitchell G. Weiss . . . . . (Sep) 265
Health and Aging of Urban American Indians (Cross-cultural Medicine—A Decade Later—Special Issue), B. Josea Kramer . . . . . (Sep) 281
Health Care and the Role of Academic Health Centers, see *'R' Word—'Rationing' of*
Health Care Reform, see *Costs and Coverage—Pressures Toward*
Health Care Use by Human Immunodeficiency Virus-Infected Students at a California Student Health Service, Charles L. Bennett, Helen Chang, Deborah Shlian, Jo Ann Dawson, Brian R. Edlin . . . . . (Jul) 41
Health Food Hazard, see *Another*
Health Issues of Afghan Refugees in California (Cross-cultural Medicine—A Decade Later—Special Issue), Juliene G. Lipson, Patricia A. Omidian . . . . . (Sep) 271
Health Leadership—A Continuing US Challenge, see *(Global)*
Health Policy and Ethnic Diversity in Older Americans—Dissonance or Harmony? (Cross-cultural Medicine—A Decade Later—Special Issue), Linda A. Wray . . . . . (Sep) 357
Hemoglobinopathies, see *Future Prospects for Treatment of*
History and Diagnosis (Correspondence), Faith Fitzgerald . . . . (Jul) 87
David R. Gutknecht . . . . . (Jul) 87
Human Immunodeficiency Virus-Infected Students at a California Student Health Service, see *Health Care Use by*
Human Immunodeficiency Virus, see Micobacterium avium *Complex and* Mycobacterium tuberculosis *in Patients Infected With the*
Human Immunodeficiency Virus Infection on the Distribution and Outcome of Pneumonia in Intensive Care Units, see *Effect of*
Hyperglycemia, see *Reflections on the Anion Gap in*
Hypernatremia, see *Diffuse Demyelinating Lesions of the Brain After the Rapid Development of*
Hypokalemia as a Cause of Tetany, Mark J. Ault, Joel Geiderman . . . . . (Jul) 65
Hypoparathyroidism Discovered During Concurrent Central Nervous System Disease, see *Long-standing Latent Idiopathic*
Hyposplenism—Persistent Uncertainties, see *Complications of Asplenia and*
Hypotension, see *Orthostatic*

I

Idiopathic Hypoparathyroidism Discovered During Concurrent Central Nervous System Disease, see *Long-standing Latent*
If Syncope, Think QT (Correspondence), Marvin L. Auerback (Jul) 87
Infancy, see *Whooping Cough in*
Infant Mortality, see *Business of Preventing African-American*
Intensive Care Unit, see *Quantitative Quality Assurance in a Community Hospital Pediatric*
Intensive Care Units, see *Effect of Human Immunodeficiency Virus Infection on the Distribution and Outcome of Pneumonia in*
Intravenous Fluoroquinolone?, see *Do We Need an*
Iranian Culture, see *Dysphoria and Somatization in*
Isolation of *Borrelia burgdorferi* From Ticks in Southern California, Hildy B. Meyers, Douglas F. Moore, George Gellert, Gary L. Euler, Thomas J. Prendergast, Maher Badri, James P. Webb, Carrie L. Fogarty . . . . . (Oct) 455

K

Korean-American Family, see *This, That, and the Other—Managing Illness in a First-Generation*

L

Labor at Home, see *Maternal Death Due to Rupture of a Low Transverse Cesarean Section Incision During*
Laotian Refugees, see *Use of Traditional and Modern Health Services by*
Laser Therapy in Gastroenterology, see *Endoscopic*
Laser Therapy in the 1990s, see *You Light Up My Life . . . and Liver—Gastroenterologic*

Latino Elders, see *Getting By at Home— Community-Based Long-term Care of*
Lead Poisoning in California, see *Exaggerated Threat of Childhood*

Lessons From the Practice:

Clinical Note—Doctor-Patient Bonding, Ralph Crawshaw . . . (Aug) 201
Man Who Would Not Die, C. Gresham Bayne . . . . . (Dec) 685
Quality Medicine, Robert L. Goldstone . . . . . (Jul) 88
Suitcase Full of Pills, Richard E. Waltman . . . . . (Oct) 474
Victor, Harland Goldwater . . . . . (Aug) 202

Leukemoid Reaction, see *Adult Still's Disease Presenting as Fever of Undetermined Origin in a Patient With*
Let's Not Do With Euthanasia What We Did With Abortion (Correspondence), George B. Markle IV . . . . . (Nov) 592
Licensing of Tissue Banks in California (Correspondence), George W. Rutherford . . . . . (Oct) 471
Life-Support Decisions, see *Effect of Values and Cultures on*
Liver—Gastroenterologic Laser Therapy in the 1990s, see *You Light Up My Life . . . and*
Long-standing Latent Idiopathic Hypoparathyroidism Discovered During Concurrent Central Nervous System Disease, Bruce E. Wilson, Suresh Tawney . . . . . (Aug) 177
Long-term Care of Latino Elders, see *Getting By at Home—Community Based*
Lung Cavities and Cysts Due to AIDS-Related Pulmonary Infection, see *Thin-walled*

M

Make-believe Drugs, see *Clinical Studies With*
Malpractice Claims Using Quality-of-Care Characteristics, see *Predicting Risk for*
Mammography Reports—Toward Clear, Concise Clinical Descriptions, see *Screening*
Man Who Would Not Die (Lessons From the Practice), C. Gresham Bayne . . . . . (Dec) 685
Managing Illness in a First-Generation Korean-American Family, see *This, That, and the Other*
Manifestations of Adult Varicella in the United States Navy 1984-1987 (Correspondence), Nathan H. Mull, Dennis E. Amundson, Waring R. Trible, Timothy B. Call (Aug) 197
Maternal Death Due to Rupture of a Low Transverse Cesarean Section Incision During Labor at Home, Val A. Catanzarite, Erin Foster, Pam Robinette, Larry M. Cousins, Jack M. Schneider . . . . . (Oct) 454
Medical Disclosure and Refugees—Telling Bad News to Ethiopian Patients (Cross-cultural Medicine—A Decade Later—Special Issue), Yewoubdar Beyene . . . . . (Sep) 328
Medications in Older Patients, Mana Hobson . . . . . (Nov) 539
Medicine, Social Ills, and Child Health, see *Scientific*
Meningitis—A Meta-analysis of Randomized Controlled Trials, see *Dexamethasone and Bacterial*
Meningitis, see *Cerebral Infarction as a Remote Complication of Childhood* Hemophilus influenzae
Meningitis Revisited, see *Meta-analysis Redux—Steroids and*
Mental Health and Illness in Vietnamese Refugees (Cross-cultural Medicine—A Decade Later—Special Issue), Steven J. Gold (Sep) 290
Meta-analysis of Randomized Controlled Trials, see *Dexamethasone and Bacterial Meningitis—A*
Meta-analysis Redux—Steroids and Meningitis Revisited (Editorial), Peter L. Havens . . . . . (Jul) 84
Correspondence, Benjamin J. Geiman, Arnold L. Smith . . (Oct) 472
Metastatic Breast Cancer, see *Carcinocythemia—A Terminal Manifestation of*
Migrant and Seasonal Farm Workers, see *Occupational Health Programs Among*
Migrant Farm Worker in California, see *Season in the Life of a*
Modesty, Sexuality, and Breast Health in Chinese-American Women (Cross-cultural Medicine—A Decade Later—Special Issue), Bertha Mo . . . . . (Sep) 260
Molecular Mimicry—Hypothesis or Reality? (Biomedical Science), Naoyuki Tsuchiya, Ralph C. Williams, Jr . . . . . (Aug) 133
Molecular Perspectives in Regulations, Pathophysiology, and Therapeutic Applications, see *Second Century of the Antibody—*
Multiethnic Neighborhoods in San Francisco, California—The Population-Based AMEN Study, see *Risk for AIDS in*
Multiple Risk Factor Intervention Trial, see *Effects of the Mycobacterium avium* Complex and *Mycobacterium tuberculosis* in Patients Infected With the Human Immunodeficiency Virus, Karla M. Kerlikowske, Mitchell H. Katz . . . . . (Aug) 144

N

'New Habits of Mind'—Bridging the Gap Between Public Health and Clinical Medicine (Editorial), Rosemary K. Sokas . . . . (Oct) 460
Nonsteroidal Anti-inflammatory Drugs, see *Gastrointestinal Complications of*
Nuclear Medicine, see *Epitomes*

O

Obstetric Care, see *Factors Influencing Family Physicians to Continue Providing*
Occupational and Environmental Medicine Clinic, see *The 10-Year Experience of an Academically Affiliated*
Occupational Health Problems Among Migrant and Seasonal Farm Workers (Cross-cultural Medicine—A Decade Later—Special Issue), Ketty Mobed, Ellen B. Gold, Marc B. Schenker . . . (Sep) 367
Older Patients, see *Medications in*
Older Russian Emigrés and Medical Care (Cross-cultural Medicine—A Decade Later—Special Issue), Meryl Brod, Suzanne Heurtin-Roberts . . . . . (Sep) 333
Operating-Room Shoe Covers, see *Blood-Saturated*
Ophthalmology, see *Epitomes*
Orthostatic Hypotension—Causes, Evaluation, and Management (Conferences and Reviews), Alan S. Hollister . . . . . (Dec) 652
Osmotic Shifts, Metabolic Compromise, and the Vulnerability of the Pons (Editorial), Ann C. McKee . . . . . (Nov) 588
Overwhelming Postsplenectomy Infection—Still a Problem (Conferences and Reviews), Malcolm L. Brigden . . . . . (Oct) 440
Editorial, Barbara Styrt . . . . . (Oct) 461

P

Pediatric Intensive Care Unit, see *Quantitative Quality Assurance in a Community Hospital*
Peer Review Organization Perspective, see *Simultaneous Reconstruction of the Abdominal Aorta and Cholecystectomy—A*
Personal Renewal (Commentary), John W. Gardner . . . . . (Oct) 457
Pesticide Endrin, see *Seizures After Eating a Snack Food Contaminated With the*
Physical Medicine and Rehabilitation, see *Epitomes*
Physician Aid in Dying—What Doctors Say, What Patients Say (Commentary), Faye J. Girsh . . . . . (Aug) 188
Editorial Comments, Paul K. Longmore, Christine K. Cassel, Albert R. Jonsen, Faith Fitzgerald . . . . . (Aug) 190
Physician-Patient Sexual Contact—Prevalence and Problems, Nanette K. Gartrell, Nancy Milliken, William H. Goodson III, Sue Thiemann, Bernard Lo . . . . . (Aug) 139
Pills, see *Suitcase Full of*
Playing the Cost-Containment Game (Commentary), William O. Robertson . . . . . (Jul) 74
Pneumonia in Intensive Care Units, see *Effect of Human Immunodeficiency Virus Infection on the Distribution and Outcome of*

Poems:

Alphabet, Thomas Reiter . . . . . (Jul) 78
Contemplating getting back to Barra de Navidad from New York Hospital, Iris Litt . . . . . (Sep) 322
Dear John Letter to My Uterus, Donna Hilbert . . . . . (Dec) 686
Dowager's Hump, Marilyn J. Boe . . . . . (Aug) 153
In April, Hearing the News, Lyn Lifshin . . . . . (Sep) 344
The Old One and the Fish, Helen M. Copeland . . . . . (Nov) 530
Only Human, Lu Carter . . . . . (Jul) 82
Rain Dance, Jim Cody . . . . . (Sep) 374
Shadow and Echo and Jade, Lu Chi . . . . . (Sep) 300
Tell Me, Doctor, Rose Mary Prosen . . . . . (Dec) 686
This Sorrow We Are Bound to Face, Mary Balazs . . . . . (Jul) 40
Visiting Hours, Mary Engel . . . . . (Oct) 439

Policy and Ethnic Diversity in Older Americans, see *Health*
Popular Movement for Physician-Assisted Dying—What the Public Is Saying, What Physicians Are Hearing (Editorial Comment), Christine K. Cassel . . . (Aug) 191
Postsplenectomy Infection, see *Overwhelming*
Predicting Risk for Medical Malpractice Claims Using Quality-of-Care Characteristics, Sara C. Charles, Robert D. Gibbons, Paul R. Frisch, Charlene E. Pyskoty, Donald Hedeker, Navneet K. Singha . . . (Oct) 433
Pseudohypoparathyroidism, see *Chronic Atypical Seizure Disorder and Cataracts Due to Delayed Diagnosis of*
Pseudothrombocytopenia in a Child with the Acquired Immunodeficiency Syndrome, Victor K. Wong, Richard Robertson, Gail Nagaoka, Eddie Ong, Lawrence Petz, E. Richard Stiehm . . . (Dec) 668
Public Health and Clinical Medicine, see *'New Habits of Mind'—Bridging the Gap Between*
Pulmonary Function, see *Effects of the Multiple Risk Factor Intervention Trial Smoking Cessation Program on*
Pulmonary Infection, see *Thin-walled Lung Cavities and Cysts Due to AIDS-Related*
Pulse Oximeter Versus Electrocardiogram (Correspondence), Harry J. Cozen . . . (Oct) 471
Response, Kevin K. Tremper . . . (Oct) 471
Put Your Money Where Your Advice Is (Correspondence), Joseph A. Abbott . . . (Nov) 592

Q

Quality Medicine (Lessons From the Practice), Robert L. Goldstone . . . (Jul) 88
Quality-of-Care Characteristics, see *Predicting Risk for Medical Malpractice Claims Using*
Quantitative Quality Assurance in a Community Hospital Pediatric Intensive Care Unit, Barry S. Frank, Murray M. Pollack . . (Aug) 149

R

Radiation Retinopathy, Ronald W. Zamber, James L. Kinyoun . . . (Nov) 530

Radiologic Case:

Thin-walled Lung Cavities and Cysts Due to AIDS-Related Pulmonary Infection, Krishnan Padmanabhan, Sharad Vora . . . (Dec) 675

'R' Word—'Rationing' of Health Care and the Role of Academic Health Centers (Commentary), Roger J. Bulger . . . (Aug) 186
Recombinant Erythropoietin Therapy in Renal and Nonrenal Anemia (Editorial), Allan J. Erslev . . . (Aug) 195
Reconstruction of the Abdominal Aorta and Cholecystectomy—A Peer Review Organization Perspective, see *Simultaneous*
Reflections on the Anion Gap in Hyperglycemia, Joseph Varon, Michael B. Jacobs, Cynthia A. Mahoney . . . (Dec) 670
Refugee Survivors of Torture, see *Working With*
Refugees, see *Mental Health and Illness in Vietnamese*
Refugees, see *Use of Traditional and Modern Health Services by Laotian*
Refugees—Telling Bad News to Ethiopian Patients, see *Medical Disclosure and*
Rehabilitation, see *Epitomes, Physical Medicine and*
Renal Failure, see *Erythropoietin Therapy in Patients With Chronic*
Retinopathy, see *Current Management of Diabetic*
Risk for AIDS in Multiethnic Neighborhoods in San Francisco, California—The Population-Based AMEN Study, Mindy Thompson Fullilove, James Wiley, Robert E. Fullilove III, Eve Golden, Joseph Catania, John Peterson, Karen Garrett, David Siegel, Barbara Marin, Susan Kegeles, Thomas Coates, Stephen Hulley . . . (Jul) 32

S

San Francisco, California—The Population-Based AMEN Study, see *Risk for Acquired Immunodeficiency Syndrome in Multiethnic Neighborhoods in*
Scientific Medicine, Social Ills, and Child Health (Commentary), Richard E. Behrman . . . (Jul) 74
Scombroid-Fish Poisoning—Underreporting and Prevention Among Non-Commercial Recreational Fishers, George A. Gellert, John Ralls, Corwin Brown, James Huston, Robert Merryman . . . (Dec) 645
Screening Mammography Reports—Toward Clear, Concise Clinical Descriptions, William H. Hindle . . . (Aug) 152
Season in the Life of a Migrant Farm Worker in California (Cross-cultural Medicine—A Decade Later—Special Issue), Juan Vicente Palerm . . . (Sep) 362
Seasonal Farm Workers, see *Occupational Health Problems Among Migrant and*
Second Century of the Antibody—Molecular Perspectives in Regulation, Pathophysiology, and Therapeutic Applications (Conferences and Reviews), Moderator: Jonathan Braun; Discussants: Andrew Saxon, Randolph Wall, Sherie L. Morrison . . . (Aug) 158
Seizure Disorder and Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism, see *Chronic Atypical*
Seizures, see *Another Health Food Hazard—γ-Hydroxybutyrate-induced*
Seizures After Eating a Snack Food Contaminated With the Pesticide Endrin—The Tale of the Toxic Taquitos, Kirsten Waller, Thomas J. Prendergast, Alan Slagle, Richard J. Jackson . . (Dec) 648
Sexual Contact, see *Physician-Patient*
Sexuality, and Breast Health in Chinese-American Women, see *Modesty,*
Shoe Covers, see *Blood-Saturated Operating-Room*
Simultaneous Reconstruction of the Abdominal Aorta and Cholecystectomy—A Peer Review Organization Perspective, William H. Heydorn, William H. Moncrief, Jr. . . . (Nov) 569
Smoking, see *Getting Some Breathing Room—Persuading Patients to Stop*
Smoking Cessation, see *Effects of the Multiple Risk Factor Intervention Trial*
Social Ills, and Child Health, see *Scientific Medicine,*

Special Series:

Costs and Coverage—Pressures Toward Health Care Reform, Philip R. Lee . . . (Nov) 576
Editorial . . . (Nov) 584

State AIDS Drug Program Expansion (Correspondence), Wayne E. Sauseda . . . (Dec) 683
Steroids and Meningitis Revisited, see *Meta-analysis Redux*
Still's Disease Presenting as Fever of Undetermined Origin in a Patient With Leukemoid Reaction, see *Adult*
Students at a California Student Health Service, see *Health Care Use by Human Immunodeficiency Virus-Infected*
Submersion Injuries in Children Younger Than 5 Years in Urban Utah, Lloyd R. Jensen, Scott D. Williams, David J. Thurman, Patricia A. Keller . . . (Dec) 641
Successful Treatment of Markedly Symptomatic Patients With Type II Diabetes Mellitus Using High Doses of Sulfonylurea Agents (Correspondence), Mayer B. Davidson . . . (Aug) 199
Suicide—What Euthanasia Activists Say, What People With Disabilities Say, see *Assisted*
Suitcase Full of Pills (Lessons From the Practice), Richard E. Waltman . . . (Oct) 474
Sulfonylurea Agents, see *Successful Treatment of Markedly Symptomatic Patients With Type II Diabetes Mellitus Using High Doses of*
Surgeon, see *Earthquakes and the Office-Based*
Syncope, see *If*
Syphilis Epidemic, see *Controlling a*

T

The 10-Year Experience of an Academically Affiliated Occupational and Environmental Medicine Clinic, Linda Rosenstock, William Daniell, Scott Barnhart, Bert Stover, Joseph Castorina, Susan E. Mason, Nicholas J. Heyer, Rebecca Hubbard, Joel D. Kaufman, Carl A. Brodkin, Matthew Keifer . . . (Oct) 425
Editorial, Rosemary K. Sokas . . . (Oct) 460

Tetany, see *Hypokalemia as a Cause of*

Thin-walled Lung Cavities and Cysts Due to AIDS-Related Pulmonary Infection (Radiologic Case), Krishnan Padmanabhan, Sharad Vora . . . . . (Dec) 675

This, That, and the Other—Managing Illness in a First-Generation Korean-American Family (Cross-cultural Medicine—A Decade Later—Special Issue), Soo-Young Chin . . . . . (Sep) 305

Ticks in Southern California, see *Isolation of* Borrelia burgdorferi *From*

Tissue Banks in California, see *Licensing of*

Torture, see *Working With Refugee Survivors of*

Toxic Taquitos, see *Seizures After Eating Snack Food Contaminated With the Pesticide Endrin—The Tale of the*

Translation is Not Enough—Interpreting in a Medical Setting (Cross-cultural Medicine—A Decade Later—Special Issue), Linda Haffner . . . . . (Sep) 255

Treatment Strategies in the Prevention of Tuberculosis (Editorial), Thomas L. Petty . . . . . (Oct) 463

Tuberculosis Chemoprophylaxis, Shelley Salpeter . . . . . (Oct) 421
Editorial, Thomas L. Petty . . . . . (Oct) 463

U

Urban American Indians, see *Health and Aging of*

Urinary Tract Infections in Children—An Update (Conferences and Reviews), Israel Zelikovic, Raymond D. Adelman, Paul A. Nancarrow . . . . . (Nov) 554
Editorial, Mary Ann Carmack, Ann M. Arvin . . . . . (Nov) 587

Use of Traditional and Modern Health Services by Laotian Refugees (Cross-cultural Medicine—A Decade Later—Special Issue), Stuart C. Gilman, Judith Justice, Kaota Saepharn, Gerald Charles . . . . . (Sep) 310

V

Varicella in the United States Navy 1984-1987, see *Manifestations of Adult*

Victor (Lessons From the Practice), Harland Goldwater . . . . (Aug) 202

Vietnam, see *Friendship Bridge to*

Vietnamese Refugees, see *Mental Health and Illness in*

Virginia, see *Ehrlichiosis in a Visitor to*

W

Wake Up and Smell the Coffee—Caffeine, Coffee, and the Medical Consequences (Conferences and Reviews), Tony Chou. . . . (Nov) 544
Editorial, Martin G. Myers . . . . . (Nov) 586

'What Kind of Work Do You Do?' (Correspondence), Jean Spencer Felton . . . . . (Oct) 469

Whooping Cough in Infancy (Correspondence), Wain Allen, Cynthia Campbell Barnes . . . . . (Dec) 681

Women, see *Cancer Screening in*

Words, see *Beyond*

Working With Refugee Survivors of Torture (Cross-cultural Medicine—A Decade Later—Special Issue), Barbara Chester, Neal Holtan . . . . . (Sep) 301

Y

You Light Up My Life . . . and Liver—Gastroenterologic Laser Therapy in the 1990s (Editorial), Richard A. Kozarek . . . . . (Jul) 83

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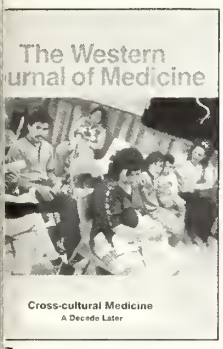

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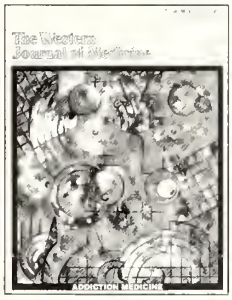

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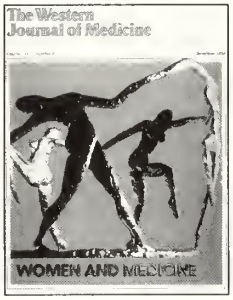

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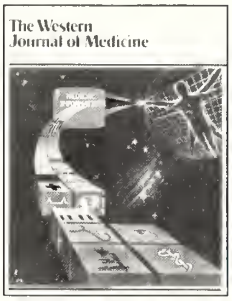

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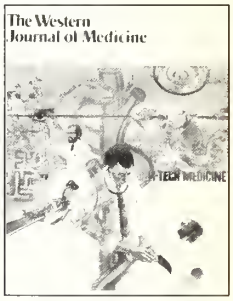

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FAMILY PRACTICE RESIDENCY FACULTY POSITION. FULL-TIME ASSISTANT PROFESSOR. UNIVERSITY OF WYOMING FAMILY PRACTICE RESIDENCY PROGRAM - CASPER. The University of Wyoming Family Practice Residency Program at Casper is a well established Family Practice residency program with 24 residents and nine faculty members known for developing outstanding rural physicians. Casper is centrally located in the state and is home to the Wyoming Medical Center, the affiliated hospital for the program, and the major medical referral center for the state. Casper offers the advantages of living in a small city that lacks the usual urban problems. Responsibilities include resident supervision in ambulatory and inpatient settings, participation in clinical research projects, direct patient care, and administrative duties. Requirements include Board Certification, a minimum of three years' experience in Family Practice, including Obstetrics, and a strong desire to teach rural Family Medicine. Applicants should include current CV and three references. Competitive salary and benefits. Come join us in beautiful Wyoming. The University of Wyoming is an equal opportunity/affirmative action employer. Final approval will be made by the University of Wyoming. Please contact Joe Schoeber, MD, Acting Program Director, University of Wyoming, Family Practice Residency Program - Casper, 1522 E. A St, Casper, WY 82601; (307) 266-3076.

GILROY, CALIFORNIA. BC INTERNIST to join established but growing private practice in Gilroy, California. Ideal candidate will have one to two years practice experience. Guaranteed salary and benefits. Excellent practice opportunity in this growing community. Send CV to Number 272, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BEAUTIFUL BOULDER, COLORADO! Position available for BC/BE Family Practice physician to join two other physicians in busy Family Practice setting. Competitive salary and excellent benefits package which includes malpractice insurance coverage. Send CV to K. Lewis, Assistant Office Manager, 1600 28th St, Ste 262, Boulder, CO 80301, c/o Health Watch Medical Center; (303) 444-6400.

ASSISTANT/ASSOCIATE CLINICAL PROFESSORS. Two positions are available in the Department of Medicine, Division of General Internal Medicine/Geriatrics of the University of California, San Diego. Candidates must be highly skilled practitioners and teachers of General Internal Medicine or Geriatrics. Position involves substantial amount of clinical practice, including managed care, both with and without housestaff. Research opportunities are available. Must have California medical license or eligible to apply. BC/BE in Internal Medicine required. Salary and rank commensurate with candidate's experience and established UCSD salary scales. Reply by 1/15/93 to Joe Ramsdell, MD, UCSD Medical Center, Dept of Medicine (8415), 225 Dickinson St, San Diego, CA 92103-8415. AA/EOE.

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PHYSICIAN OPPORTUNITIES IN CALIFORNIA AND NATIONWIDE

Call (800) 727-2478 or FAX your CV in complete confidence to (408) 727-7390. Never a fee to the physician. **Nugent & Grant, 1400 Coleman Ave, Ste B22, Santa Clara, CA 95050.**

ENDOCRINOLOGIST. Excellent opportunity to assume practice of retiring partner in Internal Medicine/Endocrinology group. Prestigious area of southern California. January 1993. Salary guaranteed and partnership opportunity available. Reply to Number 277, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INTERNAL MEDICINE – Southern California. Challenging career opportunities for specialists in Internal Medicine desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PEDIATRICIANS–Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

OB/GYN–Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

THINK ABOUT IT!! Arizona needs Primary Care physicians in several underserved areas. From northern plateaus to southern plains, both urban and rural–solo to multispecialty. Great family lifestyle, full benefits, excellent salaries. Write Bill De Long, Catalina Professional Recruiters, PO Box 12650, Tucson, AZ 85732, or call (800) 658-9166.

PUGET SOUND–WASHINGTON STATE. FAMILY PRACTICE independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attn: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

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(Continued on Page 700)

(Continued from Page 699)

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Several positions available to join a multispecialty group, partnership as well as solo practice for the explosive growth of our area population. BC/BE physician in such specialties as:

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Janis Pryor, Director Business Development/Provider Relations
or Julie Wagner, Provider Relations Coordinator
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(714) 883-8711, ext 3063

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San Jose's leading multispecialty group is growing. We are seeking BC/BE physicians in the following specialties:

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If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Maureen Forrester, San Jose Medical Group, Inc*, 45 S. 17th St, San Jose, CA 95112; **or call (408) 282-7833.**

*An independent physician group affiliated with Stanford University Medical Center.

CALIFORNIA. Central Sierra foothills group practice is actively recruiting several Family Practitioners and General Internists. Limited call, salary or guarantee, generous remuneration package with unlimited potential. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411, or FAX (415) 399-0411.

CALIFORNIA–MONTEREY BAY. ENT. Solo ENT, beginning fellowship January 1993, seeks one year coverage by physician of same specialty. Fully equipped hi-tech office located in exclusive medical complex. Excellent partnership opportunity. Mild climate enhances coastal exploration. Call (408) 459-9656 and send CV and inquiries to PO Box 2571, Santa Cruz, CA 95063-2571.

INTERNAL MEDICINE–NEVADA, TEXAS, LOUISIANA, FLORIDA! Private practice opportunities available in Las Vegas and Reno, Nevada; Dallas, Victoria, and McAllen, Texas; New Orleans and Shreveport, Louisiana; West Palm Beach, Hollywood and Plantation, Florida. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Ft Worth, TX 76185, or FAX (817) 927-0030.

PRIMARY CARE IN THE PACIFIC NORTHWEST. Diverse opportunities for Family Physicians in urban and rural health centers throughout Washington, Oregon, Idaho, and Alaska. Loan repayment possible. Practice where it's nearly perfect. Send CV to Sarena Seifer, MD, Northwest Regional Primary Care Association, 4154 California Ave, SW, #7, Seattle, WA 98116; (206) 932-2133.

HAWAII. FAMILY PRACTITIONER WITH OB SKILLS and Internal Medicine physician needed for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Puanani Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792. (808) 696-7081.

ASSOCIATE DEAN AND PROGRAM DIRECTOR. UNIVERSITY OF WYOMING FAMILY PRACTICE RESIDENCY PROGRAM AT CASPER. The Associate Dean and Program Director at the University of Wyoming Family Practice Residency Program at Casper oversees a well established, fully accredited program. This position carries the responsibilities of academic and administrative leadership, as well as teaching and research. Casper is centrally located in the state and is home to the Wyoming Medical Center, the affiliated hospital for the program, and the major medical referral center for the state. Casper offers the advantages of living in a small city that lacks the usual urban problems in an area that offers four season recreational activities. Minimum qualifications include a Doctor of Medicine degree from an approved US college of medicine; BC in Family Practice; eligibility for licensure in the state of Wyoming; and hospital staff privileges at the Wyoming Medical Center, including Obstetrical privileges. A background in Family Practice education, research, and academic administration is also required. The successful candidate should have strong interpersonal and organizational skills. Please send a cover letter of application, a CV, and the names and addresses of three references to Joseph F. Steiner, PharmD, Chairman, Associate Dean Search Committee, University of Wyoming, Family Practice Residency Program at Casper, 1522 E. A St, Casper, WY 82601. The University of Wyoming is an equal opportunity, affirmative action employer.

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Physicians HIV

The California Department of Corrections has a number of positions available for California licensed Infectious Disease Physicians at our California Medical Facility Correctional Hospital in Vacaville. The Hospital is located midway between San Francisco and Sacramento. Additional positions exist for Internal Medicine Physicians. Excellent salary & benefits. For further information for full-time or part-time opportunities, Call:

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Or send Curriculum Vitae to: **California Department of Corrections, Division of Health Care Services, Attn: CMF ID Physician Recruitment, P.O. Box 942883, Sacramento, CA 94283-0001**; FAX (916) 322-5864.

California Department of Corrections

SALT LAKE CITY–URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

TWO BC/BE OB/GYNs with commitment to caring for the underserved, needed to join 13 physician (OB, Family Practice, Pediatrics, Internal Medicine), Primary Care community health clinic in Toppenish and Grandview, Washington, which has a four physician team (Family Practice, OB, Internal Medicine). Rural setting, beautiful sunny central Washington near Columbia River Gorge. Diverse cultural influences (Hispanic and Native American). Recreational opportunities including fishing, skiing, and bikers' paradise. Competitive salary with excellent benefit package including vacation up to 32 days per year and paid professional liability. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

(Continued on Page 701)

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(Continued from Page 700)

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FAMILY PHYSICIAN–LEWISTON, IDAHO
Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson; or call (208) 743-8416.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

NORTHERN CALIFORNIA – MEDICAL DIRECTOR UR/QA. 200-bed community hospital in the San Francisco bay area seeks a Director of Medical Quality. Ideal candidate understands private practice, QA/UR, risk management, JCAH. Ability to influence and communicate effectively with medical staff is a must. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411, or FAX (415) 399-0411.

INTERNAL MEDICINE BC/BE OPENING due to retirement. Very stable multispecialty group in growing area. Will join department of eight other Internal Medicine physicians. New building on hospital campus. McHenry Medical Group Inc, Attention Thomas Wallace, MD, PO Box 576566, Modesto, CA 95357.

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PHYSICIANS WANTED

PHYSICIAN, MEDICAL DIRECTOR

Idaho's Department of Health and Welfare, State Hospital North, has an opportunity for a physician as Medical Director for a 75-bed adult substance abuse and psychiatric treatment hospital. Primary responsibilities include patient medical diagnosis and treatment; medical consultation; shared on-call; employee wellness and infection control. Small facility allows for progressive and innovative practice and a participative management style. Competitive salary; relocation assistance; excellent benefit package. Rural setting located at the base of the Selway-Bitterroot Wilderness Area. Experience Idaho – it's what America used to be! Contact Marvin Lambrecht, Administrator, State Hospital North, PO Box 672, Orofino, ID 83544; (208) 476-4511.

EOE/MF/HC/VET

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

SAN FRANCISCO BAY AREA. Family Practice and Fortune 500 Industrial Occupational clinic and hospital-based recovery unit needs associate in San Francisco bay area. Request BC/BE Family Practitioner or Osteopath for busy, lucrative practice in weather-prime area. Guaranteed salary and incentives. All offers considered and negotiable. Call Jenelle, (510) 680-8933.

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OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

PEDIATRICIANS–NEVADA, CALIFORNIA, LOUISIANA, TEXAS! Private practice opportunities available. Hospital sponsored with coverage or join an established group. For details, call Eloise Gusman, (800) 535-7698 or send CV to PO Box 101656, Ft Worth, TX 76185, or FAX (817) 927-0030.

MOUNTAIN VIEW. BC/BE Family Physician to join thriving four member Family Practice group located in the heart of the Silicon Valley. Practice includes Surgery and Obstetrics. C-sections are OK. Excellent salary and benefits. Contact Dianne Higgins, MD, 253 Franklin St, Mt View, CA 94041; (415) 967-5591.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

(Continued on Page 702)

PROGRAM MANAGER

Infectious Disease Unit

The California Department of Corrections, Division of Health Care Services, is accepting curricula vitae from Physicians interested in the Senior Program Manager position for HIV and Infectious Disease Unit. Sacramento based location.

This is the Lead Manager position for statewide HIV program administration and HIV-ID Training for the California Department of Corrections.

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Division of Health Care Services Recruitment
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The deadline for submitting classifieds for the **February** issue of WJM is **December 17.** Send your advertisement to:

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NEW MEXICO! FHP. One of America's most progressive HMOs, is seeking a BC/BE Internist to join its 28 member group in Albuquerque (population 500,000). You'll enjoy big city advantages plus small town friendliness. Deliver in/outpatient care in well-equipped, modern facilities. Emphasis on quality care, personalized patient services. Guaranteed salary, generous retirement, malpractice and comprehensive benefits provided Contact Mary Consie, (800) 444-4347, or write FHP, 4300 San Mateo NE, Albuquerque, NM 87110. EOE.

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Eight person General Internal Medicine group seeks additional physicians to join their managed care practice. 30 hour work-week, salary plus productivity, benefits, low buy-in (optional). Wanda Parker, E.G. Todd Physician Search; (800) 221-4762.

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PUGET SOUND. BE/BC Family Practitioners to staff walk-in clinics affiliated with 95 physician multispecialty group, located 30 miles north of Seattle. Opportunity for exceptional personal and professional lifestyle. Position offers competitive salary with excellent benefits. Available winter 1992 and summer 1993. Send CV to J. G. Finley, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201.

BC/BE FAMILY PHYSICIAN to join three other Family Practitioners, OB/GYN, Internist, and Physician Assistant at busy Migrant/Community Clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work, and Emergency coverage. Excellent relationship with well trained BC Family Practitioners and surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation liberal. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Personnel Assistant, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

PHYSICIANS WANTED

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA. MEDICAL/LEGAL EVALUATIONS. Opportunities in San Jose, Capitola, Salinas, Fremont, San Ramon, Oakland, San Francisco, Marin, Santa Rosa, and Sacramento for BC/BE physicians in all medical specialties. California license required. Excellent opportunity to supplement income. Send inquiry and CV to Linda Lowery, QMA, 2131 The Alameda, Ste A, San Jose, CA 95126.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

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NORTHERN CALIFORNIA. Opportunities available with Comprehensive Medical Evaluations in Sacramento and San Jose for BC physicians in Orthopedic Surgery, Psychiatry, Internal Medicine, and subspecialties, Dermatology, Neurology, Physical Medicine/Rehabilitation, Ophthalmology, Otolaryngology, Plastic/Reconstructive Surgery and Toxicology/ Occupational Medicine, to perform forensic medical evaluations. This is an excellent opportunity to supplement income without increasing your practice overhead. Send inquiry to Terence Doyle, Comprehensive Medical Evaluations, 87 Scripps Dr, Ste 308, Sacramento, CA 95825; or call (916) 567-3411.

NEVADA–GASTROENTEROLOGIST. BC/BE needed to join General Intern practice in southern Nevada. Generous salary leading to full partnership. Interest in Internal Medicine preferred. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

PALO ALTO MEDICAL CLINIC, a 150 physician multispecialty group with a national reputation for innovation and excellence, seeks BC Family Practice or Emergency Medicine physicians for full-time practice in Urgent Care facility. Occupational Medicine experience desirable. Competitive salary based on experience. Excellent benefits package. Two year partnership track. Please forward letter of interest and CV to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

SAN DIEGO AREA. Internist and/or Cardiologist, Pulmonologist, BC/BE, to join busy Internal Medicine/subspecialty group. Excellent income opportunity. Well-equipped office across from hospital. Send CV to Box 250, 647 E St, Chula Vista, CA 91910.

FAMILY PHYSICIAN OR INTERNIST to join six physician practice in lovely coastal community 25 miles south of San Francisco. Flexible schedule. CV to Dr Larry Casalino, Coastside Medical Clinic, 225 S Cabrillo Highway, Half Moon Bay, CA 94019.

INTERNAL MEDICINE–Southern California. Challenging career opportunities for specialists in Internal Medicine desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

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Arizona: CIGNA Healthplan, Professional Staffing, 11001 N. Black Canyon Hwy, Suite 400-49, Phoenix, AZ 85029, (800) 252-2471.

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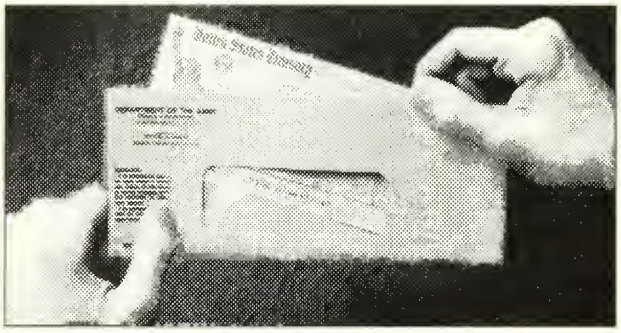

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(Continued from Page 703)

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NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

ESCAPE THOSE URBAN HASSLES and come to scenic northern California, southern California, and Phoenix, Arizona. Opportunity available to join two other Internists in private practice. Competitive salary and benefit package available. Contact Mark Oswald of Gielow Associates, 306 N Milwaukee St, Milwaukee, WI 53202; (800) 969-7715, FAX (414) 226-4131. Confidential inquiries welcome.

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(Continued on Page 705)

(Continued from Page 704)

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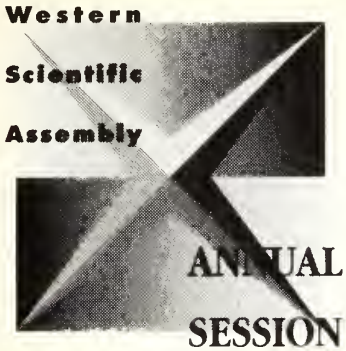

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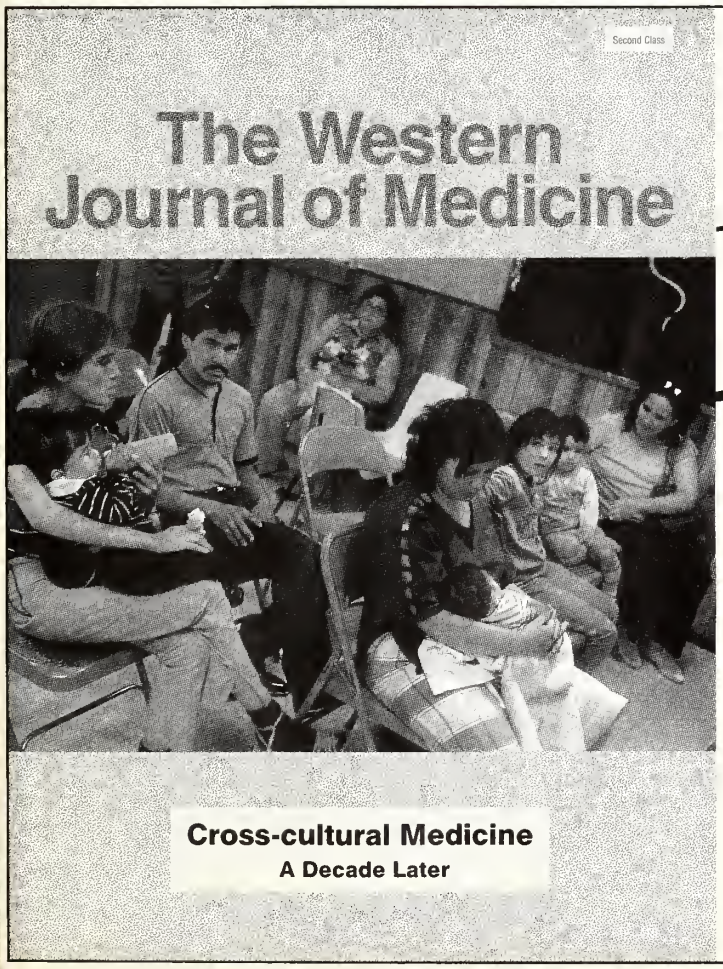

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1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

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This year's rich and varied topics include: management of pain, screening technologies and controversies, sleep disorders, skin problems of active patients, sports injuries of the brain and spine, new standards for blood-borne pathogens and CLIA, orthopedic update on the foot and ankle, ophthalmologic issues for primary care, treatment of rhinitis and sinusitis, common office gynecological problems, professional liability issues in breast cancer and implants, imaging choices 1993, management of common pediatric problems, carpal tunnel syndrome, management of difficult wound problems, HIV prevention, detection and early management, algorithms for alcoholics, management of "difficult" patients, tobacco intervention for special populations, disruptive physicians and the dilemmas for medical staff, residency selection and career planning, new frontiers in family medicine, workshops on cardiac life support and the suture course. **This is a great opportunity to earn CME Category I credit!**

OTHER EVENTS:

- **House of Delegates** will set CMA policy on health care issues facing physicians.
- **Hospital Medical Staff Section** and **Young Physicians Section** will convene their annual meetings.
- **Exhibit Hall** will feature latest medical and health care related products and services.

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